On the stereochemistry and medicinal chemistry of 6-substituted tropanes.

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Award date:
1981

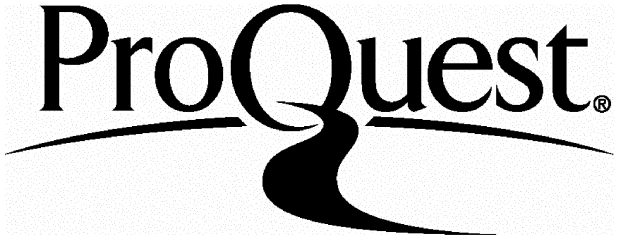
Awarding institution:
University of Bath

ON THE STEREOCHEMISTRY AND MEDICINAL CHEMISTRY OF 6-SUBSTITUTED TROPANES

THESIS

Submitted by Leung Sheh, B.Sc., M.Sc.,
for the degree of Doctor of Philosophy
of the University of Bath

1981



TO THE MEMORY OF

MY BROTHER

DAVID, MING SHEH

MY FORMER TEACHER

RIEMAN LAM

ACKNOWLEDGEMENTS

The author wishes to express his grateful thanks to Prof. Robert T. Parfitt and Dr. George H. Dewar for their initiation, encouragement and helpful advice in the course of this work.

He would like to thank the staff in the Department of Medicinal/ Pharmaceutical Chemistry especially Dr. Alan F. Casy and Dr. Mike G. Rowan for their helpful discussion in this work.

The author wishes to thank Mr. Dave Wood and Mr. Harry R. Hartell for skilled ^{1}H and ^{13}C NMR spectra respectively. He thanks Mr. Adrian Rogers for the pharmacological evaluation of the drugs synthesized.

He thanks Mrs Judy Harbutt for typing this thesis.

Finally, the author gratefully thanks the British Council and the University for some grants.

"Preserve sound judgement and discernment....."

Proverb 3.21

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SUMMARY

This thesis is composed of four parts, preceded by a brief, general introduction to the chemistry of some well-known tropanes.

In Part 1, the structure-activity relationships of pethidine-related analgesics are reviewed. The synthesis and chemistry of a novel series of narcotic analgesics based on 6-aryltropane have been reported. The analgesic activities of these drugs are reported and discussed. The chemical and biochemical aspects of the opiate receptor are also considered.

The successful resolution of (±)-6β-tropanol (51) into its enantiomers in this work has encouraged the synthesis of an enantiomeric pair of acetylcholine-like analogues. In Part 2, the chemical pharmacology of acetylcholine and its mimics is reviewed. General methods of resolution and the resolution of (±)-6β-tropanol are described. The pharmacology of these optically-active acetylcholine mimics, together with some racemic acetylcholine mimics based on (±)-6α-tropanol (106), are reported and discussed. A model for the muscarinic receptor is proposed.

Stereochemical studies on certain reductions of 6-phenyl-6-tropene (107) are reported in Part 3. Hofmann elimination and deuterium labelling experiments are described which establish the structure of the major product of lithium aluminium hydride reduction of 6-phenyl-6-tropene. This major product (123) is considered to arise by a mechanism proposed in Scheme 36. The cis-stereospecific Hofmann elimination of 6α-phenyltropane methiodide is also reported and discussed.

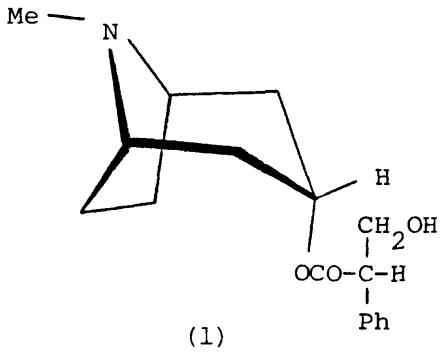
Part 4 describes the ^{1}H and ^{13}C NMR studies of a series of 6-substituted tropanes synthesized by the author. Various stereochemical aspects of 6-substituted tropanes have been investigated, including configurational determination of the 6-substituents, and N-substituent. The qualitative determination of enantiomeric purity of resolved 6β-tropanols by ^{1}H and ^{13}C NMR spectroscopy using a chiral shift reagent is described. Some new observations in shift parameters induced by chiral lanthanide reagent are reported.

A general introduction to the chemistry and stereochemistry of some well-known tropanes.

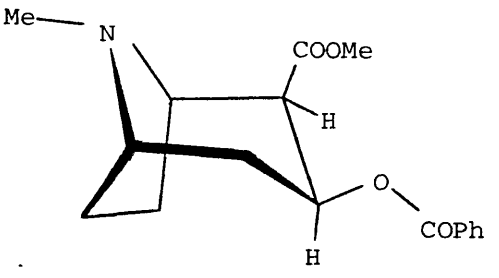
(A) Some important synthetic routes of tropanes

(a) The Robinson synthesis

The marked pharmacological activity of some naturally occurring tropanes such as atropine (racemic hyoscyamine; (1) and cocaine (2) has resulted in several decades of intensive investigation of the chemistry of the tropane series.



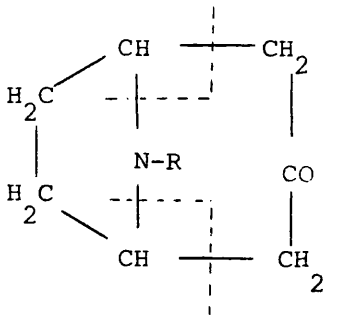
(1)



(2)

Willstätter[1] was the first chemist to synthesize tropanes. Tropinone (3; R=Me), a key degradation product obtained during the determination of the structure of atropine, was synthesized by Willstätter employing a fifteen-step route[1]. This was much simplified when Robinson[2] introduced his synthesis of tropinone in only one step. He described his inspiration as:

"By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succindialdehyde, methylamine and acetone" (see Fig. 1). Tropinone was obtained in small yield by the condensation of succinaldehyde with acetone and methylamine in aqueous solution. Replacement of acetone by calcium acetonedicarboxylate, and the use of a buffer, markedly improved the yield[2,5,6].



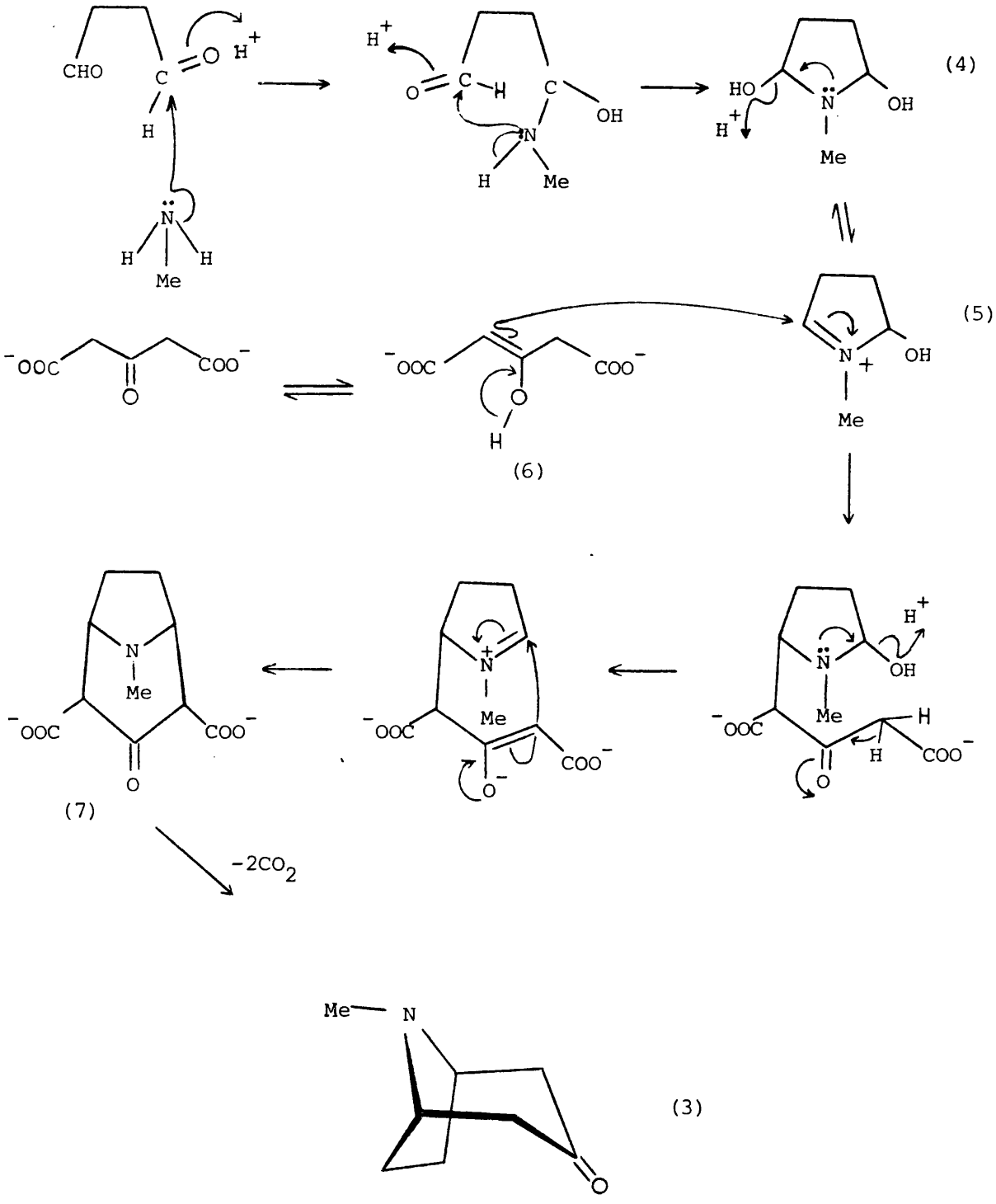
(3)

Fig. 1

The Robinson synthesis is in fact related to condensations of the Mannich type. It is suggested that cyclisation occurs between methylamine and succinaldehyde first to form the intermediates (4) and (5), (Scheme 1). The latter is an iminium species which is electron deficient and capable of attack by the enol (6) behaving as a nucleophile. Subsequent steps follow a repetition of the Mannich reaction on the alternate side of the molecule. The resulting intermediate (7), a β-keto dicarboxylic acid, readily undergoes decarboxylation to give tropinone (3; Scheme 1).

The suggestion that the formation of the 5-membered ring intermediate occurs first in the proposed mechanism (Scheme 1) has some support from the bioconversion of ornithine (8) to hyoscyamine (1)[49]. Incorporation experiments using [2-^{14}C, δ-^{15}N]ornithine, [1,4-$^{14}C_2$]-putrescine, and [4-^{3}H] N-methylputrescine (9) into hyoscyamine indicate that these precursors were all confined to the pyrrolidine moiety (Scheme 2).

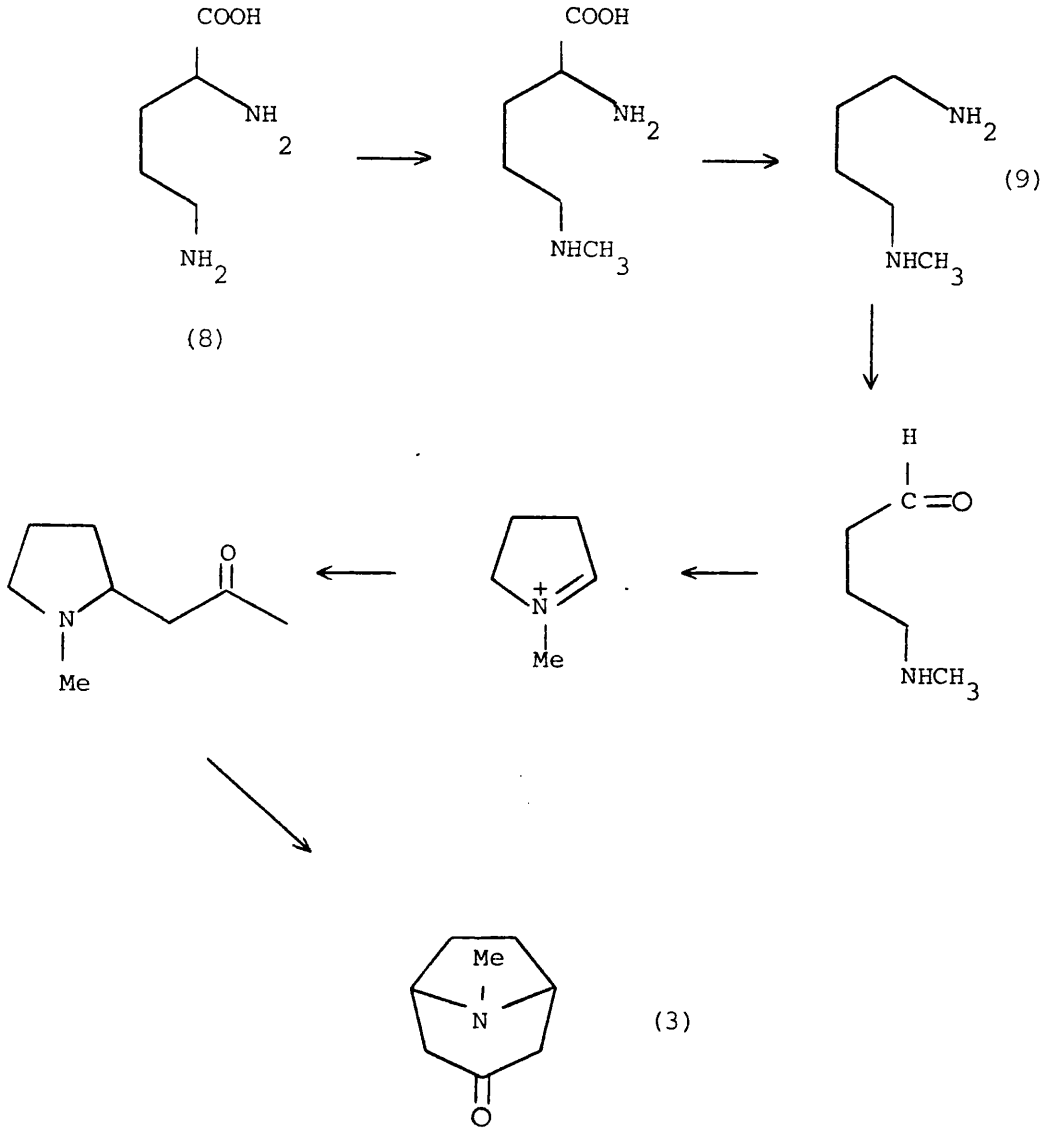
The yield of product obtained from the Robinson synthesis was


CHO
C
O
H+
H
N
H
H
Me
H+
C
H
O
C
OH
N
H
Me
HO
H+
N
OH
Me
(4)
(5)
-OOC
COO-
O
-OOC
COO-
O
H
(6)
N+
OH
Me
H+
N
OH
Me
-OOC
COO-
H
H
O
N+
Me
-OOC
COO-
O-
N
Me
-OOC
COO-
O
(7)
-2CO2

Me
N
O

(3)

Scheme 1


COOH
NH2
NH2
COOH
NH2
NHCH3
NH2
NHCH3
(9)
(8)
H
C=O
NHCH3
N+
Me
O
N
Me
Me
N
O
(3)

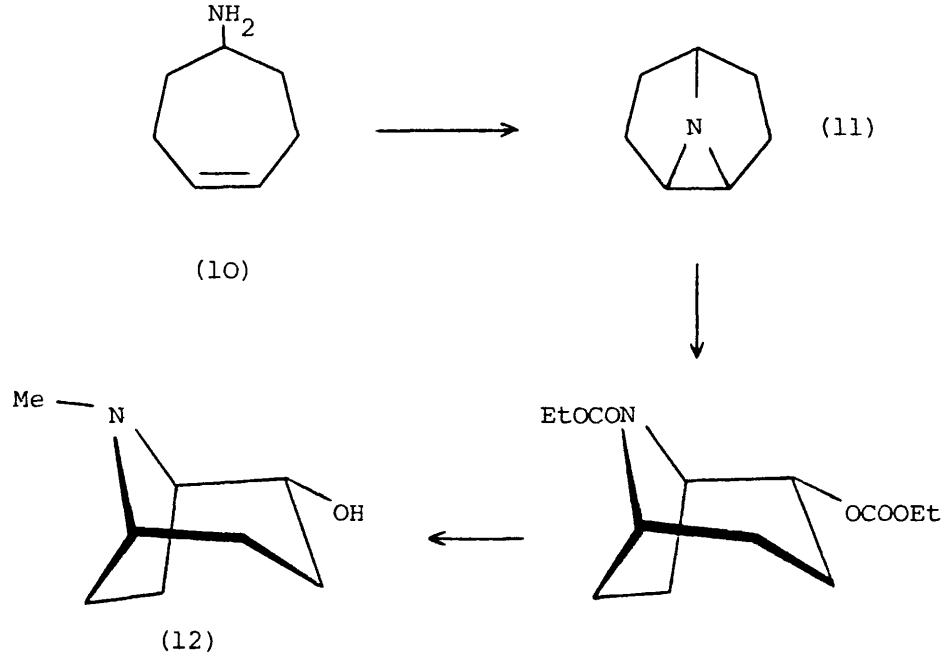
Scheme 2

later improved by Schöpf and Lehmann[5,6] who carried out the condensation using a γ-dialdehyde, acetonedicarboxylic acid and methylamine hydrochloride in a buffered medium. The use of ammonia in the Robinson synthesis led to nortropinone (3; R=H)[7] whereas the use of different alkylamines brings about variations of the nitrogen substituent[3,4].

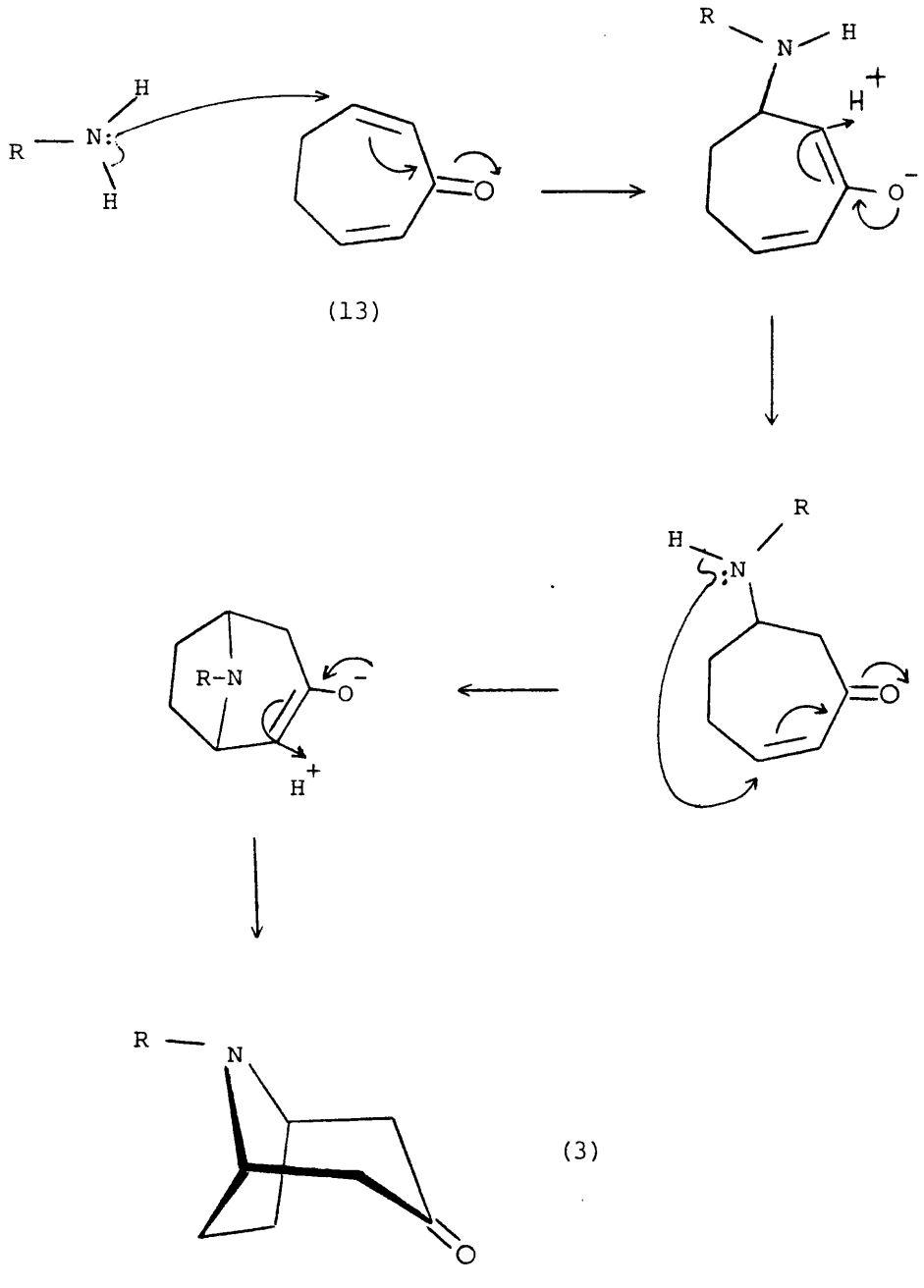
The Robinson synthesis has found wide application in the synthesis of 2-substituted tropanes, 3-substituted tropanes and 2,3-disubstituted tropanes, and is regarded as one of the most facile syntheses for tropane alkaloids (for further discussion, see Part 1).

(b) From bridged aziridines

This interesting route employes 5-aminocycloheptene (10) as the starting material and treatment with lead tetraacetate gave a bridged aziridine (11) which, when reacted with diethyl pyrocarbonate followed by lithium aluminium hydride reduction, produced (±)2α-tropanol (12; Scheme 3)[8].



Scheme 3



(13)

(3)

Scheme 4

(c) From 2,6-cycloheptadienone

This route was introduced by Bottini and Gal[10], who reacted 2,6-cycloheptadienone (13) and methanolic methylamine to give tropinone (3; R=Me) in 64% yield. The same reaction using ethylamine and benzylamine gave N-ethyl- and N-benzylnortropinones. The condensation process is in practice a double Michael addition, in which a primary amine acts as the Michael donor and 2,6-cycloheptadienone as the acceptor (Scheme 4).

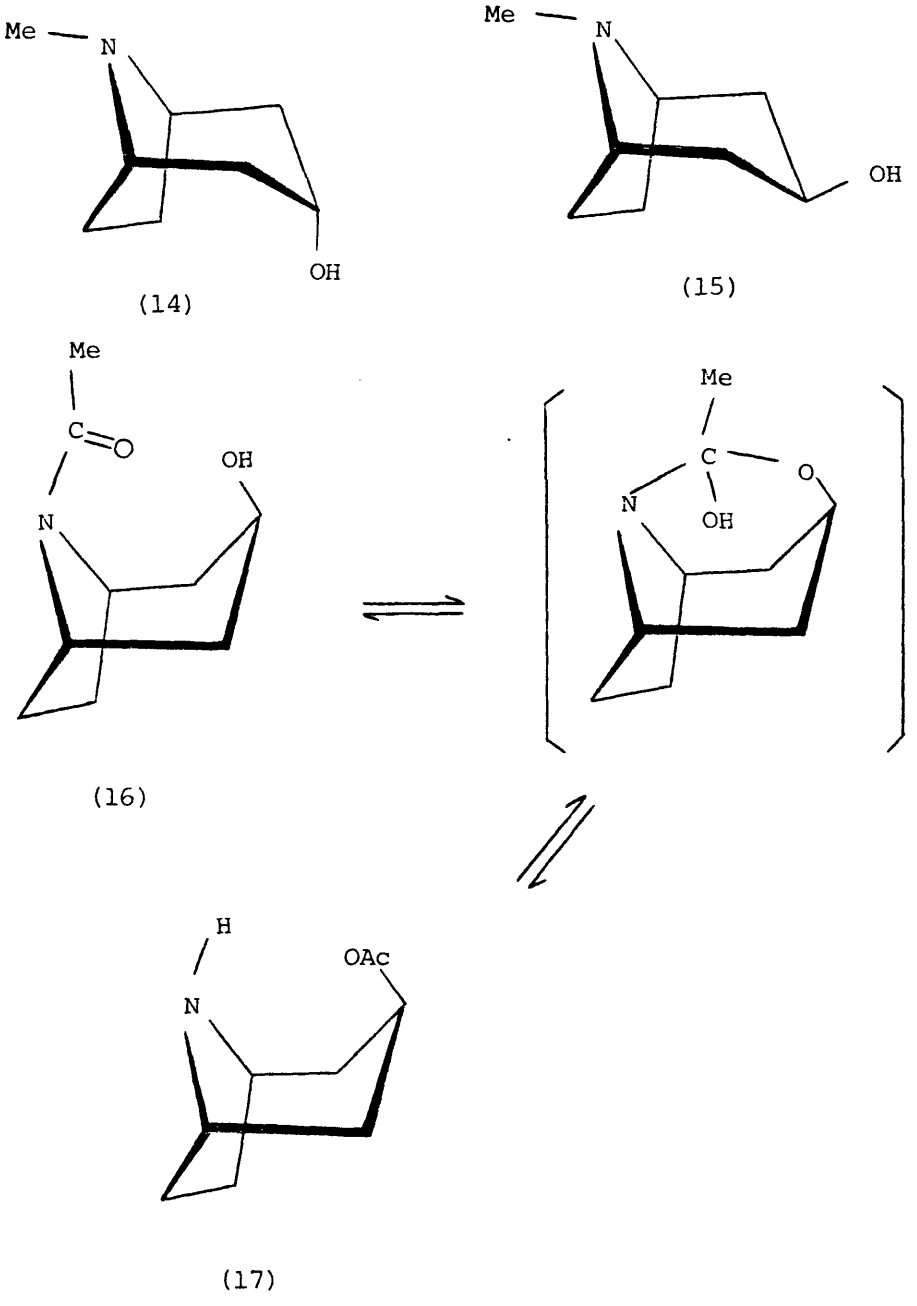
(B) Structural elucidation of some well-known tropanes

The structure and stereochemistry of naturally occuring tropanes were investigated intensively in the early 50's. Conclusive evidence for the structure of atropine[11,12], scopolamine[13] and valeroidine[14] have been obtained by total synthesis. The stereochemistry of these tropanes have been explored by classical chemical methods.

(a) Tropine and ψ-tropine

Tropine (14) is the precursor of atropine (1) and was shown to differ in stereochemistry at the C-3 position with its epimer ψ-tropine (15) by N→O acyl migration experiments[15,16,17]. N-acetyl-nor-ψ-tropine (16) rearranged on heating at 150°C to O-acetyl-nor-ψ-tropine (17; Scheme 5) whereas the corresponding N-acetyl-nor-tropine did not undergo isomerization under identical conditions. Further evidence was obtained by heating N-benzoyl-nor-ψ-tropine and its epimer with excess of hydrogen chloride in dioxane solution under identical conditions[16]. The former rearranged into O-benzoyl-nor-ψ-tropine hydrochloride but the latter remained unchanged.

These reactions were shown to proceed only with neighbouring nitrogen and hydroxyl groups. Thus, it was concluded that nortropine and tropine have α-orientated C-3 hydroxyl groups whereas nor-ψ-tropine and ψ-tropine have the C-3 hydroxyl groups β-orientated.



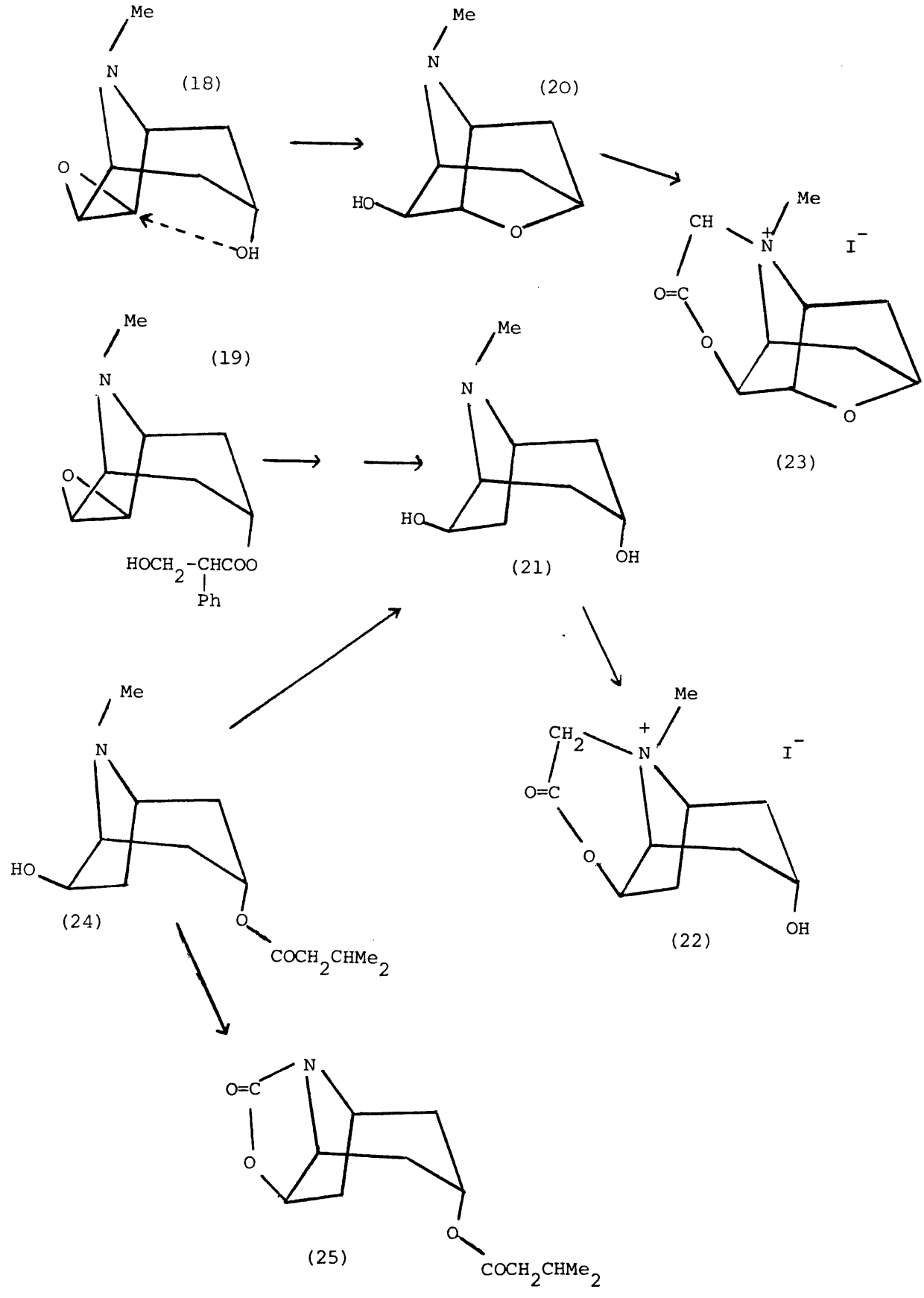
Scheme 5

(b) Scopolamine and valeroidine

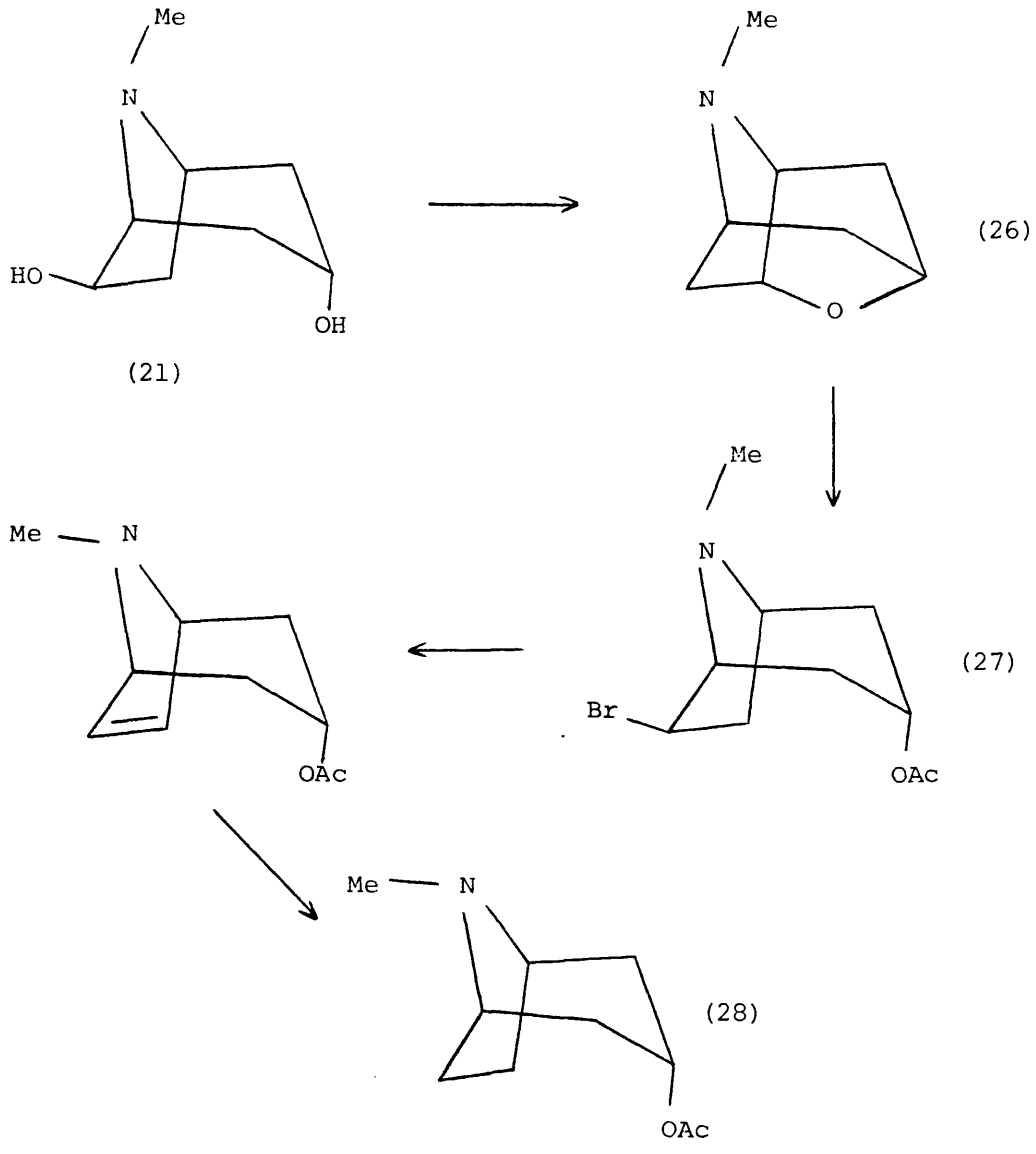
Scopine (18), the precursor of scopolamine (19), rearranged spontaneously into the tetrahydrofuran derivative scopoline (20) and this was interpreted[18-20] as an internal rearward nucleophic attack of the C-3 α-hydroxyl oxygen on the epoxide groups at C-6 and C-7. Thus, this strongly suggested that the C-3 substituent of both scopolamine and scopoline is α- and that the epoxide bridge is β-orientated. Further, hydrogenolysis of (-)-scopolamine gave the tropyl esters of (±)-trans-3,6-dihydroxytropane (21). Hydrolysis of these esters and subsequent resolution by d-tartaric acid gave the (+) and (-) enantiomers of (21)[21]; the 6β-orientation of the hydroxyl group was confirmed by conversion to the cyclic lactone salt (22) on treatment with ethyl iodoacetate. Besides, scopoline (20) also gave a lactone salt (23) on treatment with ethyl iodoacetate. Thus, the structure and stereochemistry of scopolamine and its derivatives were firmly established (see Scheme 6).

$KMnO_4$ oxidation of valeroidine (24) gave a cyclic derivative (25)[23] and this suggested the β-orientation of its C-6 hydroxyl group (Scheme 6).

The correlation of the orientation of the C-3 hydroxyl group in scopolamine and valeroidine with that of tropine was determined by converting scopolamine and valeroidine into tropine. Dehydration of (21) gave tropene oxide (26) which on acetobromolysis yielded 3α-acetyloxy-6β-bromotropane (27)[23]. Dehydrobromination and subsequent hydrogenation led to 3α-acetyloxytropane (28) which on hydrolysis gave tropine[23] (Scheme 7).


Me
N
(18)
O
OH
(20)
HO
(23)
I⁻
(19)
HOCH2-CHCOO
Ph
(21)
OH
(24)
COCH2CHMe2
(22)
CH2
O=C
(25)

Scheme 6



Scheme 7

(C) General stereochemistry of tropanes

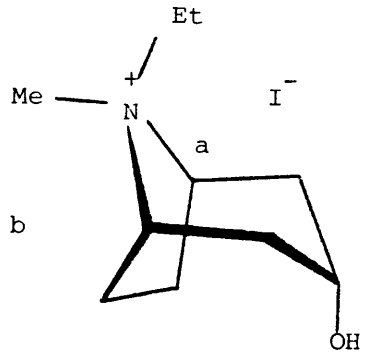
(a) N-configuration of some quaternary salts and tertiary bases of tropanes

The N-configuration of quaternary salts and tertiary bases of tropanes was the subject of much controversy in the '50's and early '60's. Foder, through the study of a number of stereospecific quat-

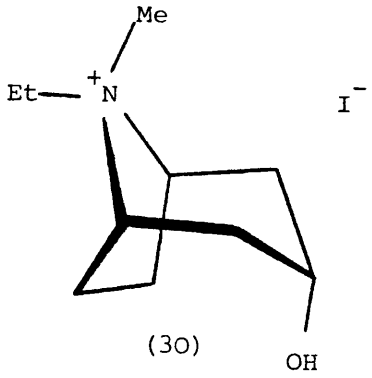
ernisations of tropanes, formulated a rule[24] stating that when two different groups are attached successively to the ring nitrogen atom of tropanes, the group entering first assumes a position towards the piperidine ring (axial) and the group entering second is fixed in the equatorial position with respect to the piperidine ring. It was considered[24] that this stereospecific selectivity is due to Pitzer strain[25] operating in the highly deformed five-membered ring of the tropanes, which forces the first N-substituent to occupy the axial position and displaces the second alkyl group to the equatorial position.

The first observation that led to the formulation of Fodor's rule was from the distinct difference of N_a-ethylnortropan-3α-ol methiodide (29) from its N-epimer tropan-3α-ol ethiodide (30). as shown by melting point, crystal form, and infrared data[26,27]. The former was formed by quaternising N-ethylnortropan-3α-ol with methyl iodide and the latter by reacting tropan-3α-ol with ethyl iodide[28].

Similarly, ψ-tropine reacted with ethyl iodoacetate to give N_b-ethoxycarbonylmethyl-ψ-tropinium iodide (31)[28], and N_a-ethoxycarbonylmethylnortropan-3β-ol with methyl iodide gave the corresponding N-epimer (32)[28]. (32), on hydrolysis gave the betaine (33) while the betaine hydrate (34) was obtained from (31). Treatment of the betaine (33) with hydrobromic or hydroiodic acid and evaporating gave the lactone (35) whereas (34) resisted lactonisation under identical conditions[28]. Thus, the N-configuration of (31) and (32) were confirmed (Scheme 8).



(29)



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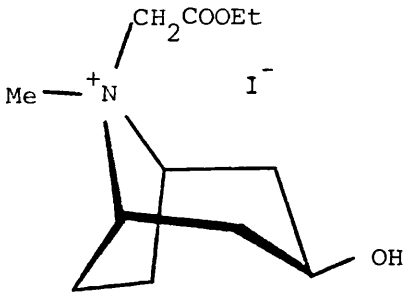

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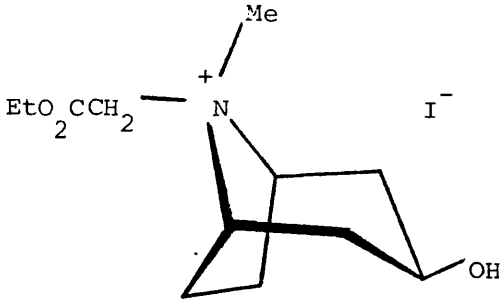

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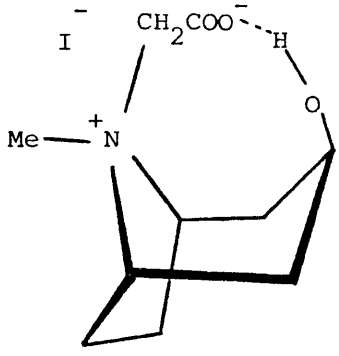

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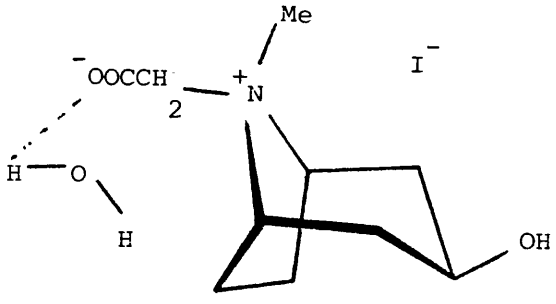
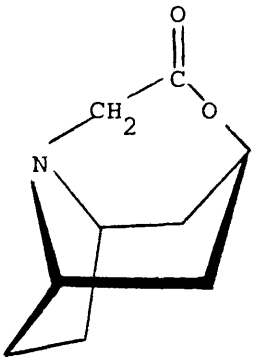


(34)

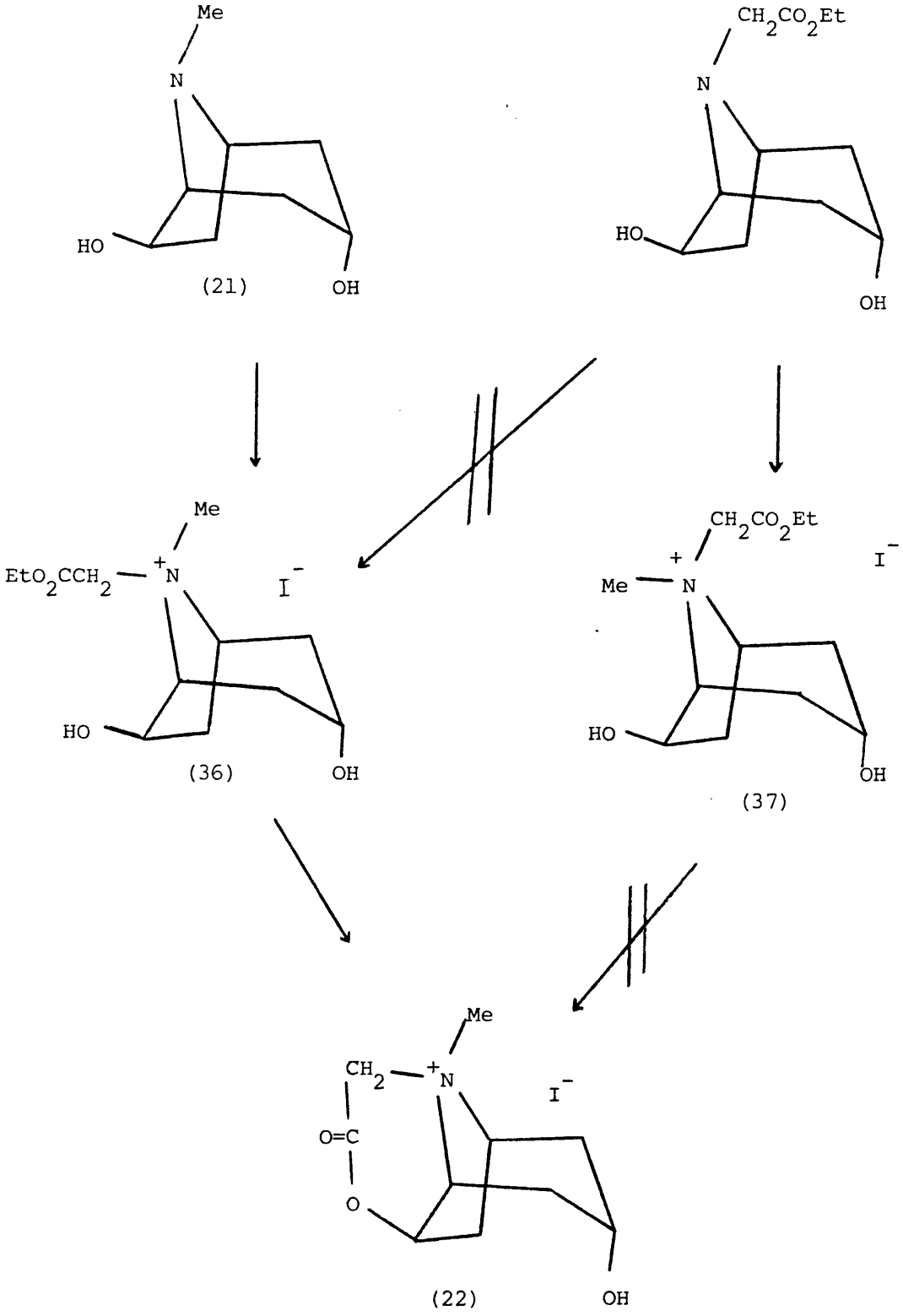
Scheme 8



(35)

Lactonisation experiments[29] were also carried out on $\underline{N}_b$-ethoxycarbonylmethyl-3$\underline{\alpha}$,6$\underline{\beta}$-dihydroxytropanium iodide (36) and its epimer $\underline{N}_a$-ethoxycarbonylmethylnortropane-3$\underline{\alpha}$,6$\underline{\beta}$-dihydroxytropanium iodide (37). The former lactonised spontaneously to give (22) while the latter resisted lactonisation under identical conditions (Scheme 9).

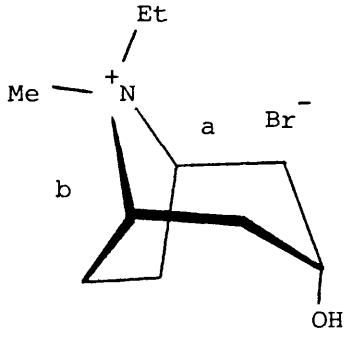
However, Fodor's "Pitzer strain" explanation of his rule[24] cannot satisfactorily explain the fact that some tropanes such as $\underline{\psi}$-tropine and $\underline{\ell}$-cocaine hydrochloride have their $\underline{N}$-methyl group orientated in the equatorial position. The argument is that if the equatorial position is less favourable for the orientation of the $\underline{N}$-methyl group than the axial one because of Pitzer strain in the five-membered ring, $\underline{\psi}$-tropine and $\underline{\ell}$-cocaine should have the $\underline{N}$-methyl group situated in the axial position instead of the equatorial position. In early '70's, Fodor[30] suggested that the diaxial interaction of the 2,4-$\underline{\beta}$-hydrogens is greater due to the flattened six-membered ring than the compression by 6,7 hydrogens of the five-membered ring on the equatorial side. Angular deformation of the five-membered ring helps to diminish this compression. In addition, he suggested that the group already covalently bound to nitrogen can


Me
N
HO
OH
(21)
CH2CO2Et
N
HO
OH
Me
EtO2CCH2
+N
I-
HO
OH
(36)
CH2CO2Et
Me
+N
I-
HO
OH
(37)
Me
CH2
+N
I-
O=C
O
OH
(22)

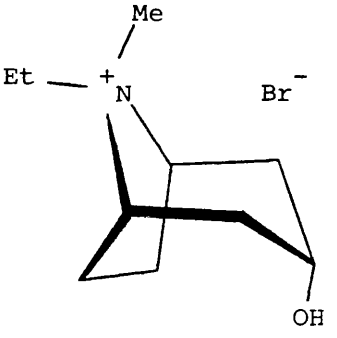
Scheme 9

endure 2,4-diaxial compression in the six-membered ring more easily than the incoming second alkyl group which is a charge-separated solvated species in the transition state of quaternisation.

To confirm the validity of Fodor's rule[24,30], $\underline{N}_a$-ethylnortropine methobromide (38) obtained by quaternising $\underline{N}$-ethyl tropine with methyl-bromide, and tropine ethobromide (39) obtained by reacting tropine with ethylbromide, were subjected to X-ray crystallographic studies[31,32]. It was found that $\underline{N}_a$-ethylnortropine methobromide has its methyl group orientated in the equatorial position whereas its $\underline{N}$-epimer has its ethyl group orientated equatorially. These findings firmly support Fodor's proposition that equatorial quaternisations is sterically preferential.



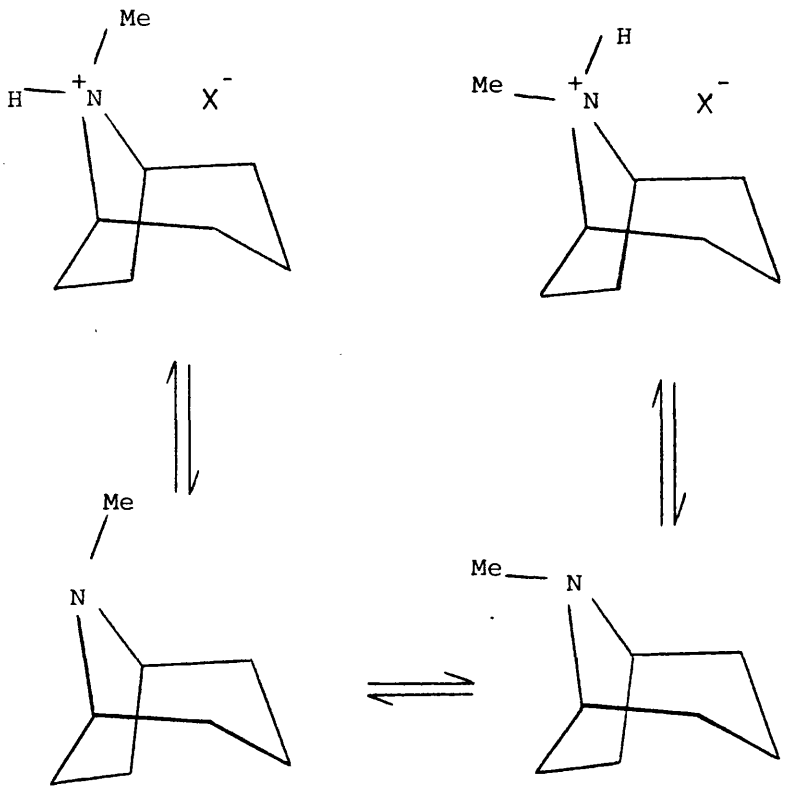
(38)



(39)

Of interest, the stereochemical process of quaternisation can be explained by the configurational equilibrium of the $\underline{N}$-methyl groups of tropanes in solution, as investigated by Closs[33] through ^{1}H NMR studies. He disagreed with Fodor's "Pitzer strain" explanation[24] which suggested that the axial $\underline{N}$-epimer is the more stable isomer. Closs pointed out that since the inversion of substituents on trivalent nitrogen in relatively unstrained systems is a process of low activation energy[34], there may be an interconversion

of the two N-epimers of tropanes in solution via the free bases in fast equilibrium (Scheme 10).



Scheme 10

The above equilibrium of tropane salts in solution is supported by ^{1}H NMR studies of ψ-tropine deuteriochloride under different conditions[33]. Closs also showed that for some tropane hydrochlorides, the major N-epimer in solution is the equatorial isomer. These findings suggested that the equatorial N-epimer is the more stable species and that the equatorial side of tropanes is the less hindered side. Thus, during quaternisation, the incoming alkyl group will preferentially attack the less hindered side. These suggestions are thus consistent with Fodor's later explanation[30].

In the crystalline state, tropanes without 6,7 substituents are likely to assume equatorial N-configurations. X-ray crystallography studies showed that for tropine[35], ψ-tropine[36] and ℓ-cocaine[37], the N-methyl groups were all equatorially orientated.

However, X-ray crystallograhic studies[38] showed that S-(-)-hyoscine hydrobromide ((-)-scopolamine) has its N-methyl group axially positioned. The preference of an unusual axial N-configuration for hyoscine is probably due to the β-orientation of the epoxide group which would generate steric repulsion and destabilize the equatorial N-epimer.

(b) Conformations of the five-membered ring and six-membered ring of tropanes

The azabicyclo[3,2,1] frame work of tropanes is formed by a nitrogen bridge fused on opposite sides of a cycloheptane ring, thus giving tropane itself a five-membered pyrrolidine ring as well as a six-membered piperidine ring with a common nitrogen bridge. In order to have better understanding of the conformations of tropanes, some relevant stereochemical aspects of pyrrolidine and piperidine are reviewed as follows.

Pyrrolidine has been shown from ESR study[39] to exist in an equilibrating half-chair form resembling that of cyclopentane. Like cyclopentane, pyrrolidine also undergoes pseudorotation[40], that is, each atom of the ring oscillates in a direction perpendicular to the average plane of the ring since the potential energy barrier is very low. It has been suggested[39] that pyrrolidine exists in a

half-chair form (three atoms in one plane and the other two outside the plane; Fig. 2).

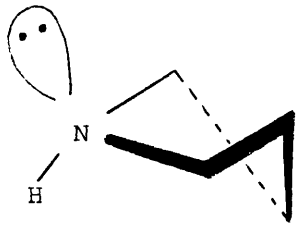


Fig. 2

These preferred conformations of pyrrolidine relieve that strain resulting from diaxial interactions between adjacent protons.

In the pyrrolidine ring of tropanes, the conformation of the ring is highly deformed because of the torsional strain of the propyl bridge in the six-membered ring acting at the 1,5 bridge-head positions. Thus, the five-membered ring of tropanes becomes geometrically constrained and assumes a rigid envelope conformation (Fig 3), quite different from that of the ordinary pyrrolidine ring.

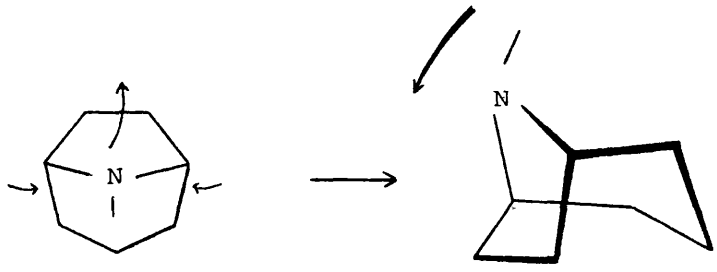


Fig. 3

The problem of the conformation of the tropane six-membered ring has aroused much controversy[41,42]. In general, a flattened or distorted chair conformation has been suggested for many

tropanes[43-47], so as to relieve severe 2,4-diaxial interactions. Besides, the ethylene bridge in the five-membered ring also compresses the 1,5 bridge-head carbon and causes the 2,4 diaxial bonds to diverge, resulting in further flattening of the chair conformation[48] (Fig. 4).

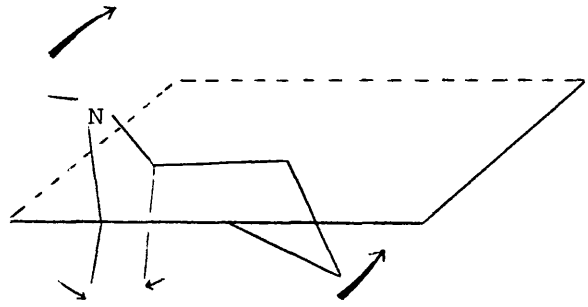
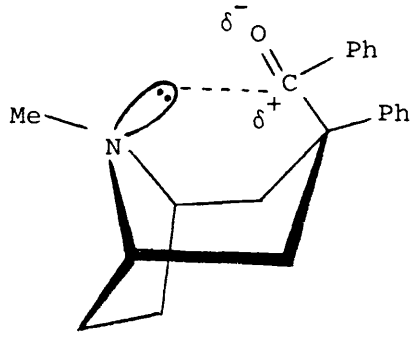


Fig. 4

However, more recently, both ^{1}H and ^{13}C NMR studies[46,47] indicate that tropanes capable of intramolecular H-bonding between the C-3 substituents and the ring nitrogen atom prefer a boat conformation. ^{13}C NMR studies indicate that 3β-benzoyl-3α-phenyltropane (40) exists in a boat conformation, whereas the tropane carboxylate (41; R=Et) has a flattened chair conformation[47].



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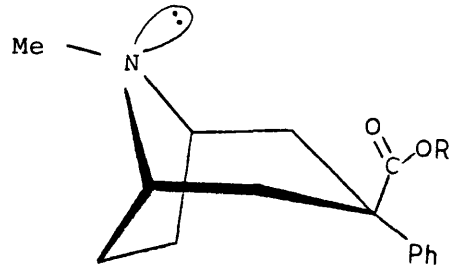
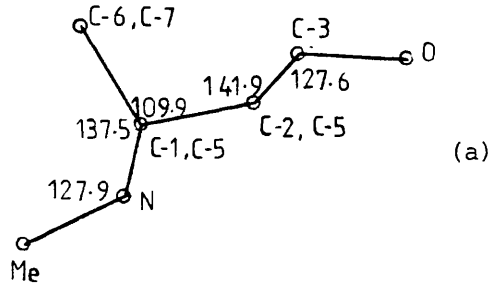


(41)

The actual molecular dimensions and stereochemistry of tropanes, as exemplified by ψ-tropine, emerged from the X-ray crystallographic analysis of Schenk et al.[36]. These studies indicated that the ethylene bridge of ψ-tropine flattens the chair conformation of the six-memberedring considerably by bringing C-1 and C-5 closer together. The angle between planes in the six-membered ring of (C-1)-(C-2)-(C-3) is widened to 141.9° (Fig. 5a).The ethylene bridge also tends to decrease the valency angle of (C-5)-N-(C-1) to only 102.3°, and the internal angle of the bridge to 103.3° (Fig. 5b). The five-membered pyrrolidine ring assumes an angularly deformed conformation with an angle of 137° (Fig. 5 a).



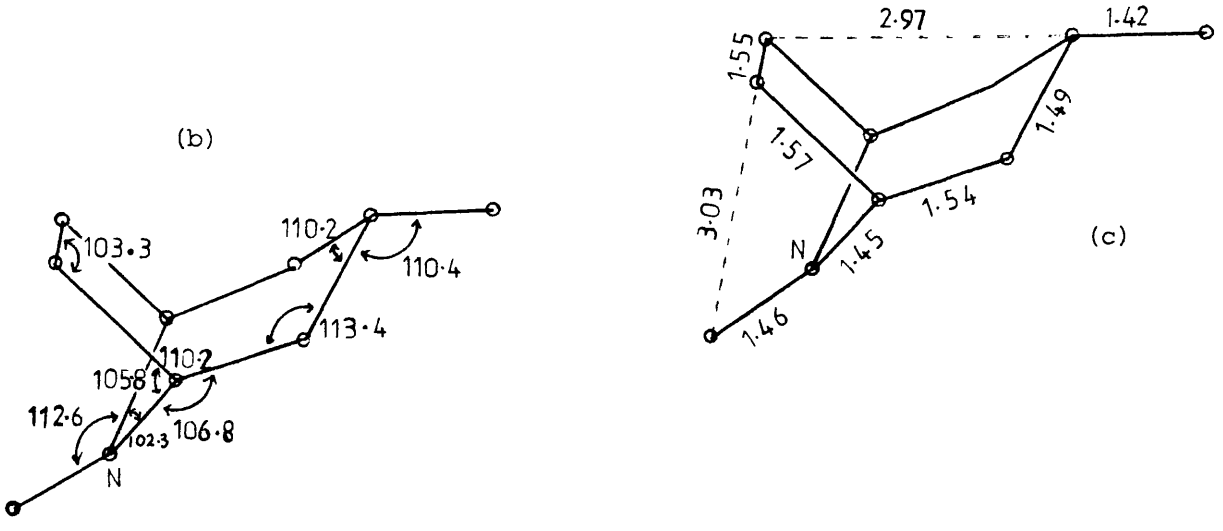


Fig. 5. Solid state structure of ψ-tropine, (a) angles between planes in the molecule perpendicular to the mirror plane; (b) inter-bond angles; (c) bond distances and some interatomic distances.

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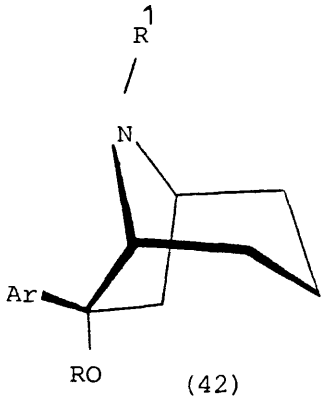
Part 1. Some potential narcotic analgesics based on

6β-aryl-6α-tropanols

1.1 Introduction

The structural resemblance of esters of 6β-aryl-6α-tropanols (42: R = hydrogen, acyl; R^1 = methyl, phenylalkyl alkyl etc.; Ar = aryl) with the reversed ester of pethidine (43) and pethidine (44) encourages research into these tropanes as potential analgesics[1].



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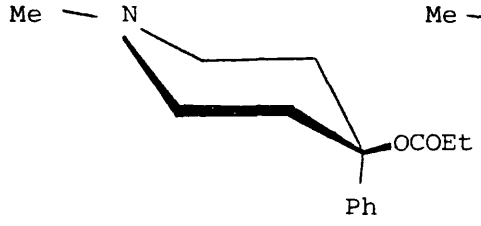

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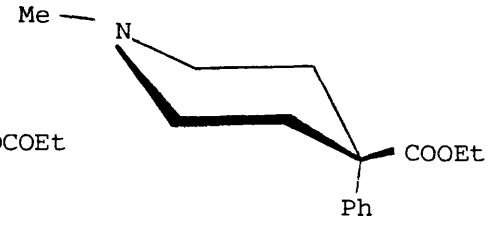
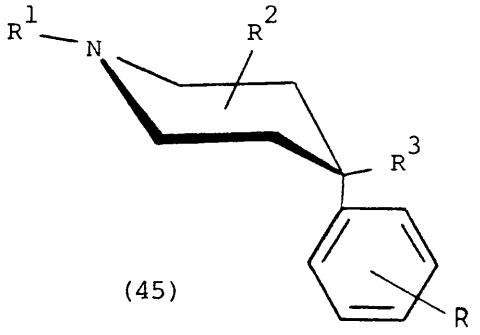


(44)

Since little research has been done on narcotic analgesics based on 3-substituted tropanes and 6-substituted tropanes, the general structure-activity relationships are reviewed on the 4-phenylpiperidine class of analgesics which have undergone intensive investigation.

Numerous pethidine-related compounds have been produced since the first synthesis of pethidine by Eisleb[2] in 1941. This group of compounds has the general structure represented by (45; R^1, R^2 = hydrogen, alkyl, phenylalkyl etc.; R^3 = carbalkoxy, acyloxy, alkyl ether groups etc.; R = OH, H) and was suggested[3] to bear certain configurational analogies with morphine (46).

Pethidine has a potency graded between morphine and codeine, with lower toxicity and shorter drug action than morphine[4], and



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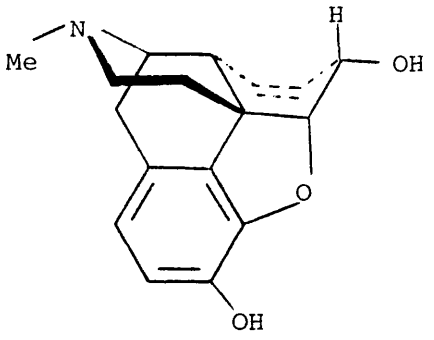


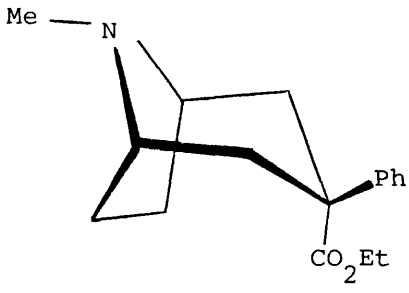
(46)

has achieved wide clinical acceptance[5,6]. Replacement of the N-methyl group with hydrogen or other higher alkyl groups causes decrease in potency. However, substitution with groups like phenethyl increases the potency 2 - 3 times[7], whereas the N-(2-benzoylethyl)[8] and N-(3-hydroxy-3-phenylpropyl)[9] derivatives were found to be 100 times and 150 times more potent than the N-methyl derivative respectively. The 4-carbethoxy function was found to be more active than methyl or high alkyl esters. However, reversal of the ester function increases the potency[6]. Substitutions on the 4-phenyl ring in general reduce activity. However, the m-hydroxy and O-methyl derivatives have higher potency than the parent phenyl compound[10,11].

Attempts to synthesize antagonists based on the 4-phenylpiperidine series by substituting allyl, substituted allyl and cyclopropylmethyl groups to the ring nitrogen have produced agonists that are devoid of antagonist activity[12]. The N-hexyl, N-heptyl derivatives of norketobemidones were reported to display weak antagonist activity[13].

3-Substituted tropane analogues of pethidine have been synthesized, The ethyl 3α-phenyl-3β-carboxylate tropane (41; R = Et) was reported

to have activity 1.5 times greater than pethidine[14]. The epimeric ester (47)[15] of (41; R = Et) was found to be about half as active as (41; R = Et) and more toxic.



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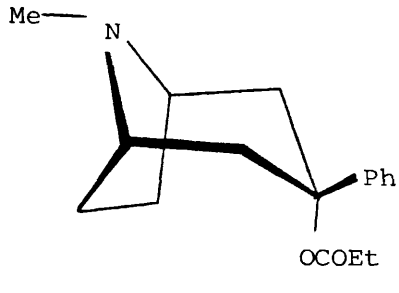


(48)

The reverse ester of (47), 3β-phenyl-3α-propionyloxytropane (48)[16], was reported to have potency similar to the carboxylate tropane derivative (41; R = Et).

The 6β-aryl-6α-tropanols and their esters on the other hand, have not been explored[1]. Because of the rigidity of the five-membered pyrrolidine ring of tropanes, substituents at the C-6 or C-7 position would be sterically constrained in a fixed, definite configuration. This would provide certain advantages for studying the interaction of the drug with the opiate receptor, and minimize the problem of the role of conformational factors in influencing analgesic activity[17,18] (also see section 1.2.1.6). The N-substituents chosen for 6β-aryl-6α-tropanol series of analgesics are similar to those employed for the 4-phenylpiperidine series.

1.2 Discussion

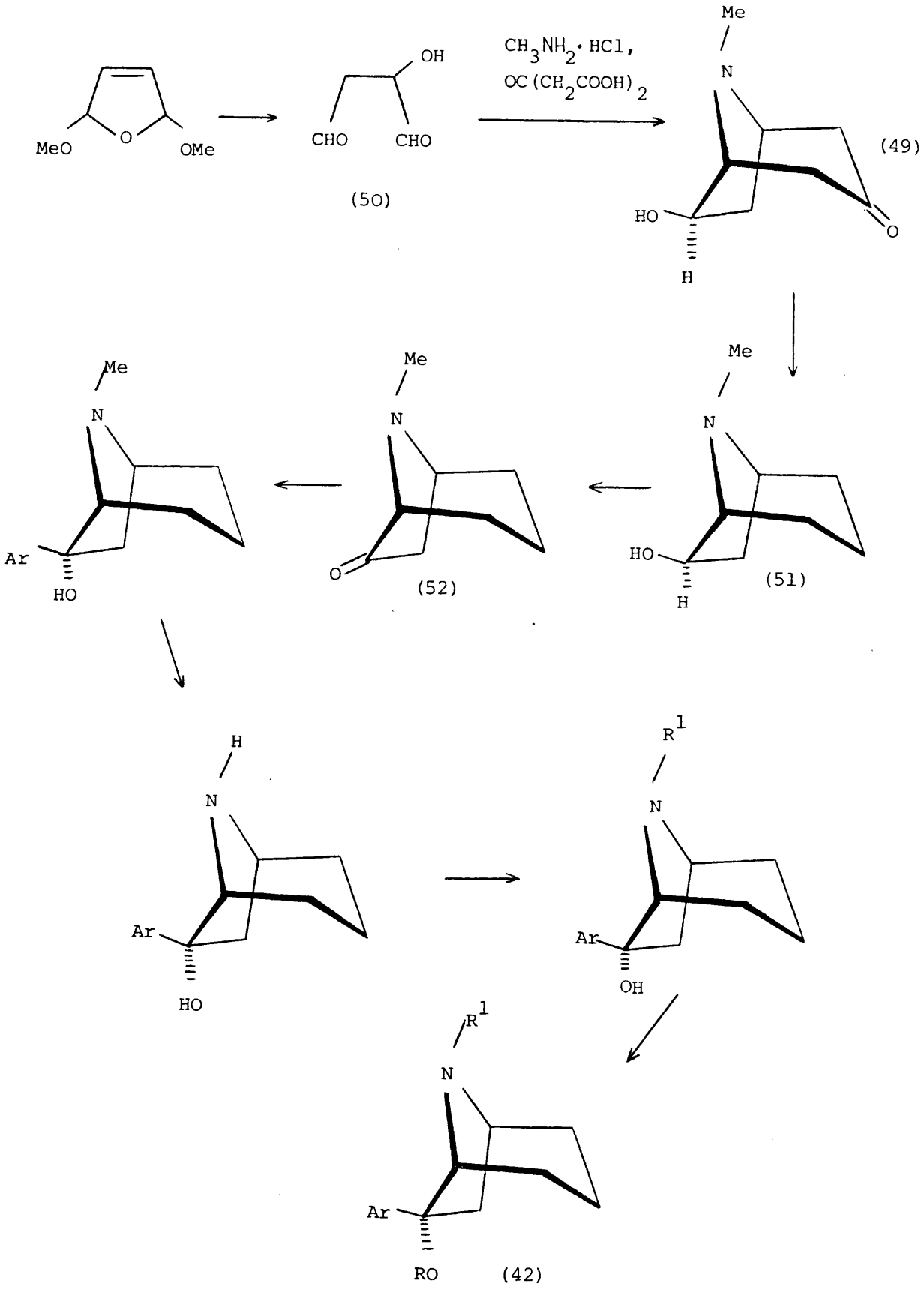
1.2.1 Syntheses and chemistry

1.2.1.1 General scheme for the total synthesis of the 6β-aryl-6α-tropanols and corresponding esters.

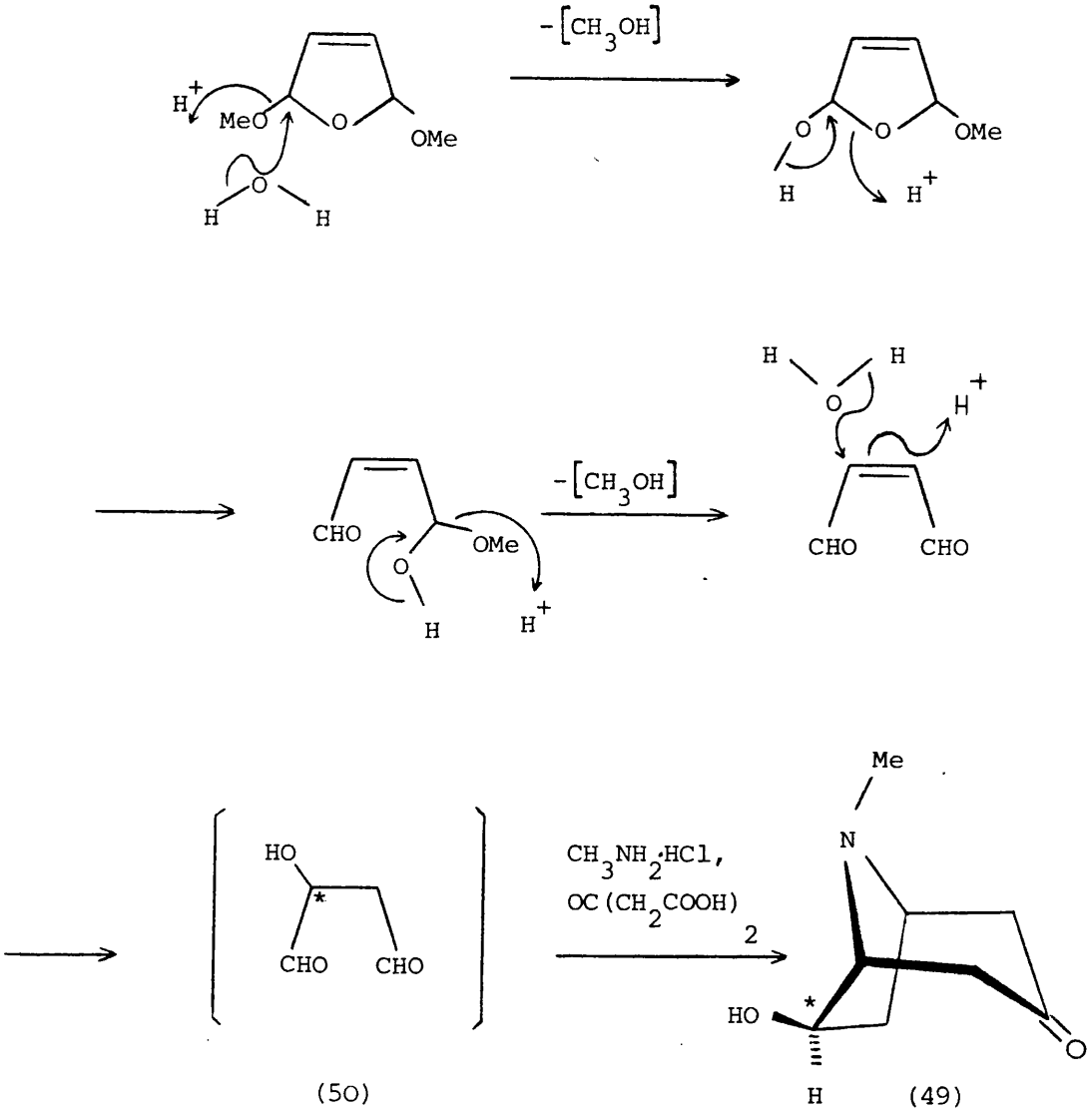
The synthetic approach to secure this series of compounds (Scheme 11) starts from the Robinson synthesis of the parent compound 6β-hydroxytropinone (49)[19, 20, 21] which involves the condensation of methylamine hydrochloride, acetonedicarboxylic acid and hydroxysuccinaldehyde (50) at a pH range of 4.0 - 5.0 at room temperature. The hydroxysuccinaldehydeis a highly reactive but unstable species, particularly at high temperature. (50) is prepared by rapid *in situ* hydrolysis of 2,5-dimethoxy- 2,5-dihydrofuran using 3 N hydrochloric acid[21] (Scheme 12). This step is, in fact, a Michael addition in which water acts as the Michael donor. The reaction is important since the water molecule has an equal chance of attack on either C-2 or C-3 of the intermediate (50), thereby generating the asymmetric centre of the 6-substituted tropanes and hence their racemic modifications (Scheme 12).

The mild conditions employed in the Robinson synthesis of this work are close to those found in physiological media and avoid side reactions such as aldol-condensation. Quantitative preparation of this ketone (49) proved impossible because of the high solubility of (49) in the aqueous reaction medium. Extraction required a prolonged liquid-liquid method. The use of large volumes of ether in the continuous extraction process also demanded great caution.

There are certain limitations to the Robinson tropane synthesis,


MeO
OMe
CHO
CHO
OH
(50)
$CH_3NH_2 \cdot HCl$,
$OC(CH_2COOH)_2$
Me
N
HO
H
O
(49)
(51)
(52)
Ar
R1
RO
(42)

Scheme 11



(50) (49)

Scheme 12

one of which is the nature of alkylamine used. It was found in this work that when benzylamine hydrochloride was used instead of methylamine hydrochloride, the synthesis did not proceed to give the corresponding N-benzyl derivative. Agocs et al.[22] have determined the marked effect of the nature of alkylamine on the yield of tropane synthesized by this method (Table 1).

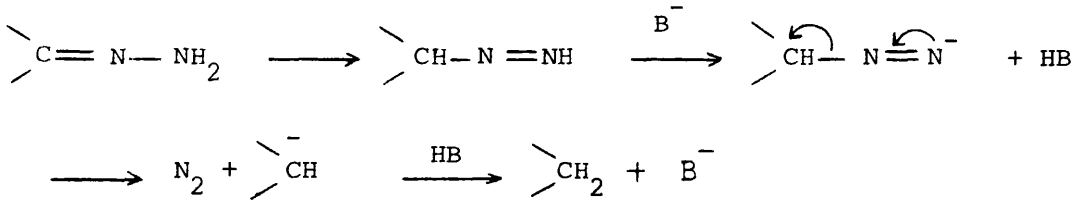
Table 1.[22]

Alkylamine	Yield of tropane (%)
Methylamine	100
Ethylamine	90
n-Propylamine	74
n-Butylamine	35
Iso-butylamine	22
Iso-propylamine	5
t-Butylamine	0

The reason for this order of reactivity is considered to be related to the steric requirement of the alkylamines[22].

The carbonyl group at the C-3 position of 6β-hydroxytropinone was then removed by Wolff-Kishner reduction[23] to afford the secondary alcohol 6β-tropanol (51). Since the bond-dissociation energy of the C=N bond of the hydrazone is quite high ($\sim$ 147 Kcal mol^{-1}), a high temperature (180 - 200°C) was required for the decomposition of the hydrazone, in the presence of a strong base such as potassium hydroxide or sodium methoxide.

The mechanism for the decomposition of the hydrazone in the Wolff-Kishner reduction is well established[24,25] (Scheme 13).



Scheme 13

The infrared spectra of 6β-tropanol and 6β-hydroxytropinone in the region of 3400 - 3650 cm^{-1} in $CHCl_3$ are very similar[23]. The -O-H stretching at 3450 cm^{-1} is indicative of intramolecular hydrogen bonding typical of amino alcohols (Fig. 5d)[26-29]. The intramolecular H-bonds in (49) and (51) also suggest the β-orientation of the 6-hydroxyl group.

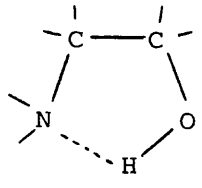


Fig. 5d.

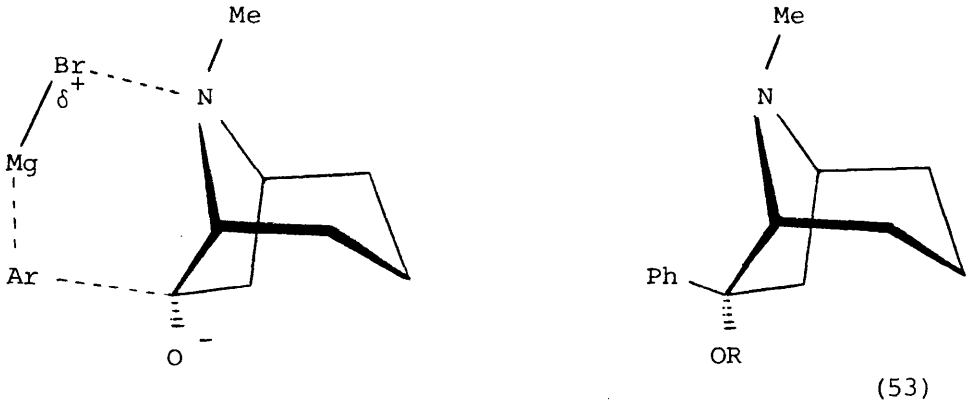
The relative configuration at the C-6 position of 6β-hydroxytropinone and 6β-tropanol is established as β- by correlation with valeroidine (24) and trans-3α,6β-dihydroxytropane (21), using chemical methods[30-32]. Further evidence of the β-configuration of the 6-hydroxy group of these compounds was obtained from ^{1}H NMR and ^{13}C NMR studies (See Part 4). The N-configuration of (49) and (51) will also be discussed in Part 4.

Chromic acid oxidation[23,33] of 6β-tropanol afforded the ketone tropan-6-one (52) which is a β-amino ketone and is rapidly oxidised by air. The unusually high absorption frequency of the C-6 carbonyl group in the infrared spectrum (1742 cm^{-1}) may be indicative of the highly deformed pyrrolidine ring[23]. Another minor peak (1670 cm^{-1}) in the infrared spectrum may suggest a degree of enol-keto tautomerism.

Grignard reactions between tropan-6-one (52) and aryl magnesium halide complexes gave the 6β-aryl-6α-tropanols (42: R = H)[1]. The alkyl halides used were bromobenzene, m-bromoanisole, p-bromoanisole and 4-bromoveratrole. The yield of 6β-phenyl-6α-tropanol (53; R = H) was over 90% whereas the yield of other 6β-aryltropanols was usually less even with a longer time of reaction. This is probably due to increased steric hindrance when more bulky aryl halides were used.

The 6-aryltropanol synthesized by these Grignard reactions are predominantly to be the 6β-aryl isomer, as shown by ^{1}H NMR analysis. It is suggested that during the transition state of the Grignard reaction there is an alignment of the arylmagnesium halide complex with the tropan-6-one molecule[1] (Fig. 6).

This stereospecific association during the transition state hence leads to a definite β-configuration of the phenyl group and an α-configuration of the hydroxy group in the reaction product. Traces of the corresponding α-phenyl isomer may also be formed. However, these cannot be isolated unless a large amount of reactants



(53)

Fig. 6

is used in the Grignard reactions, followed by chromatography.

Attempts to reverse the stereochemistry of 6β-phenyl-6α-tropanol at the C-6 position by hydration of the olefin, 6-phenyl-6-tropene using formic acid[59], sulphuric acid[59] and oxymercuration-demercuration[60,61] methods were not successful (see Section 3.2.1, Part 3).

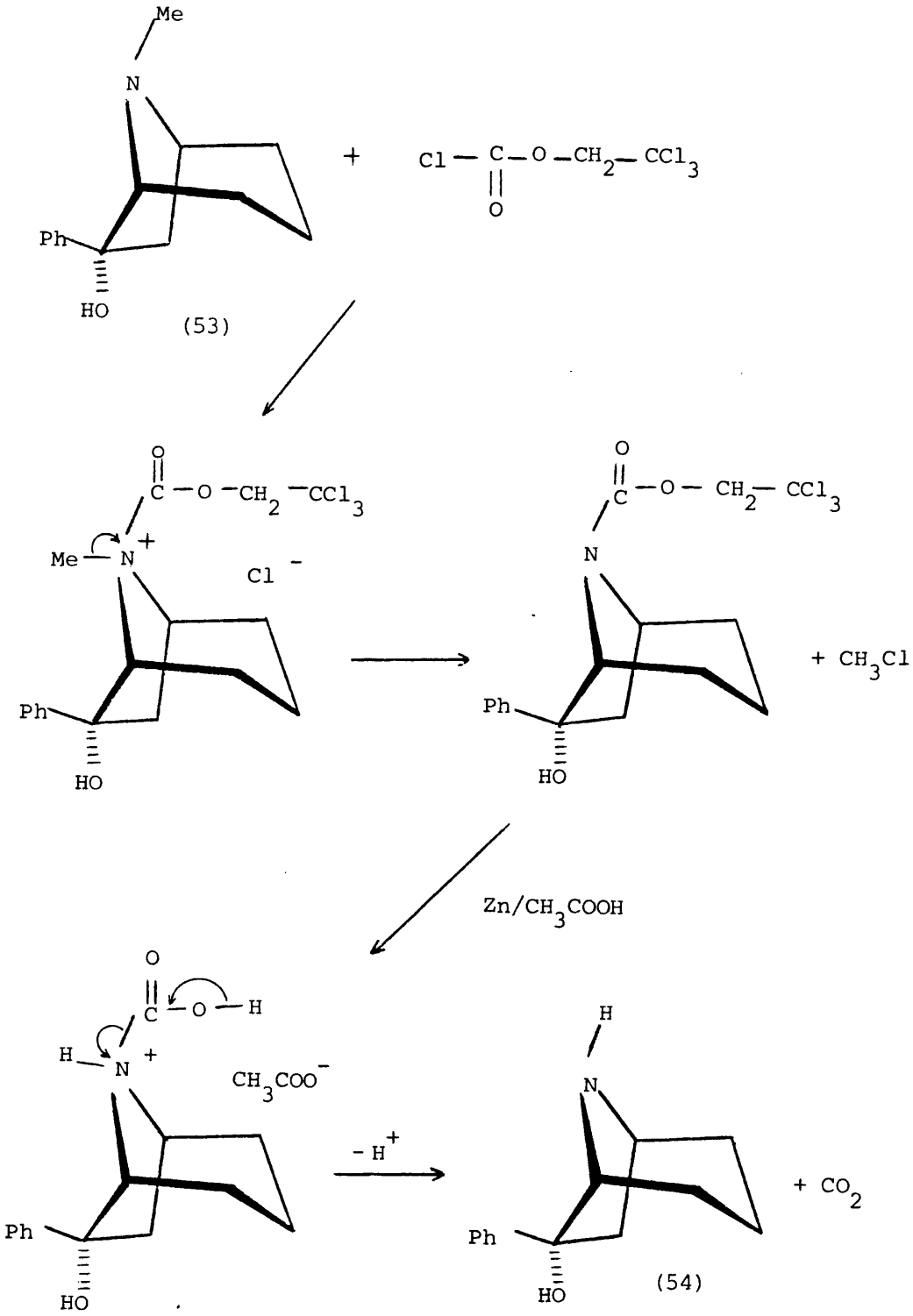
Confirmation of the β-orientation of the aryl ring comes from ^{1}H NMR studies of the tertiary base (53; R = H) and its methiodide (Part 4). The N-configuration of 6β-aryl-6α-tropanols is assigned as axial from evidence obtained from ^{13}C NMR studies of 6β-phenyl-6α-nortropanol (54) and its tertiary base (53; R = H). Detailed discussion is given in Part 4.

1.2.1.2 Synthesis of 6β-phenyl-6α-nortropanol (54) by N-dealkylation

In this work, the secondary amine (54), a key compound in the synthesis of a whole series of N-alkylated 6β-phenyl-6α-nortropanols, was obtained by N-demethylation of the tertiary amine (53; R = H) with 2,2,2-trichloroethyl chloroformate[1,34]. N-dealkylation by cyanogen bromide (the von-Braun reaction[35, 36, 40]) has been widely applied in alkaloid chemistry for opening tertiary cyclic amines. However, the yield of this reaction was often low (less than 20%)[37], and often accompanied by side products. Chloroformate esters such as ethyl chloroformate and phenyl chloroformate are now in general use since these reagents give better yields and cleaner products[34, 37, 40]. Nevertheless, one of the main shortcomings of these two reagents is the difficulty in the hydrolysis of the carbamate which often demands long periods of reflux with strong acids or strong bases in aqueous or alcoholic media[34].

Another efficient N-dealkylation reagent is vinyl chloroformate[41, 42]. This reagent was claimed to give high yields in N-demethylation reactions on certain narcotic agents[42]. However, the procedure employing vinyl chloroformate also involves the decomposition of the carbamate by bubbling anhydrous HCl through a dichloromethane medium followed by refluxing in 25% sulphuric acid[42]. This would certainly present difficulties with acid-sensitive compounds. Vinyl chloroformate is also not readily available.

The N-demethylation reagent used in this work is 2,2,2-trichloroethyl chloroformate[1, 34] which was originally used as protecting group

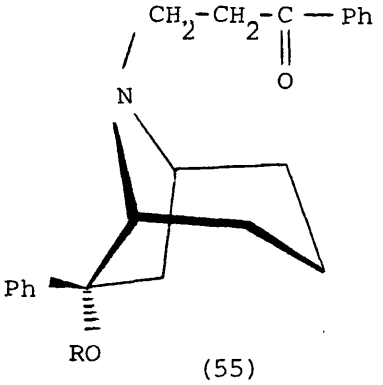


Scheme 14

for various hydroxyl and amino groups under mild conditions[43]. This N-demethylation reagent was successfully used in the demethylation of tropinone and morphine in reasonable yield[34]. The carbamates undergo facile decomposition at room temperature with zinc dust in acetic acid. In this work, the N-demethylation of 6β-phenyl-6α-tropanol proceeded smoothly to afford the corresponding secondary amine (54) in a 52 - 60% yield (Scheme 14).

1.2.1.3 Syntheses of N-(2-benzoylethyl)-6β-phenyl-6α-nortropanol (55; R = H) and N-(2-cyanoethyl)-6β-phenyl-6α-nortropanol (56; R = H) by Michael addition.

In this work, the two nortropanols (55; R = H) and (56; R = H) were obtained by Michael additions[44] of the secondary amine (54)[1] on unsaturated acceptors.



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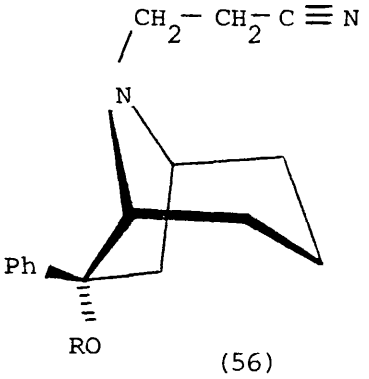
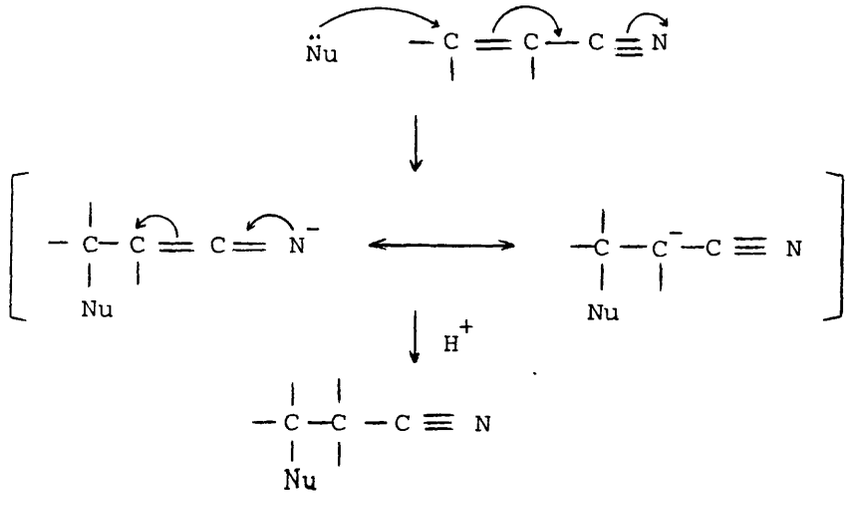


(56)

The term Michael addition was originally applied to the base-catalysed addition of an anion (donor) derived from an active α-hydrogen atom in the system O = C - CH to an ethylenic double bond of an acceptor such as conjugated unsaturated ketones. The scope of the Michael addition has broadened and can be generalised as

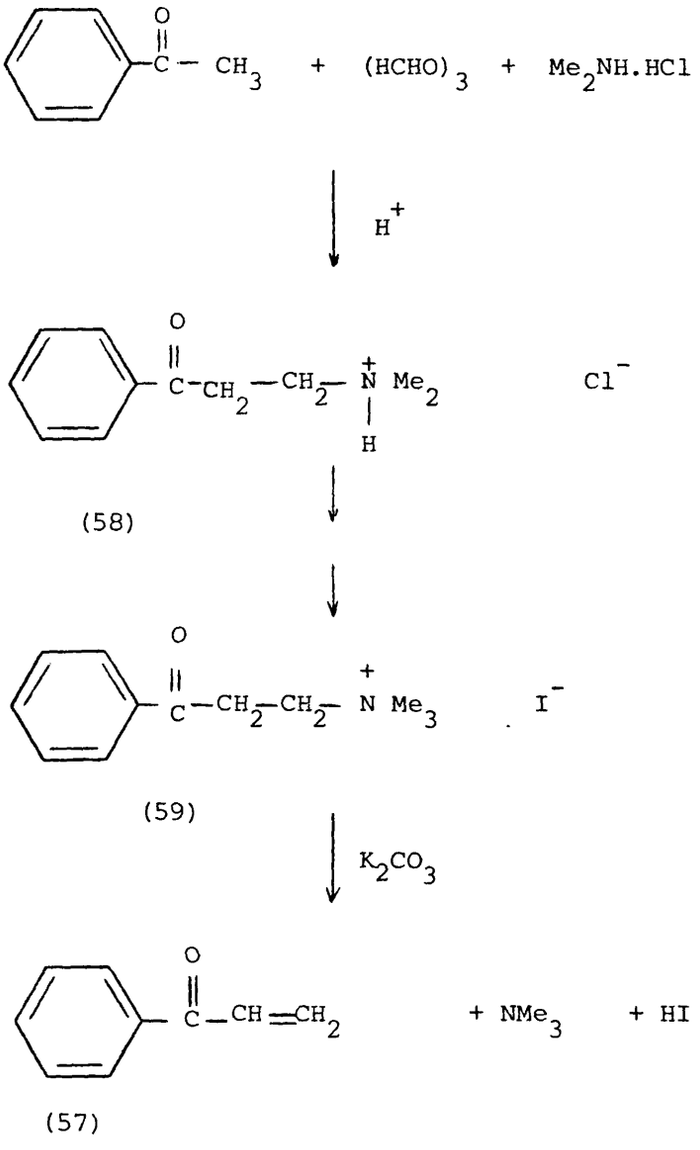
the addition of a nucleophile to a substrate of the form $-\overset{|}{C}=\overset{|}{C}-Z$[45], where Z is an electron withdrawing group (e.g. formyl, keto, cyano, nitro, carboxy, amido, amino etc.) and the nucleophile can be amines, hydrogen halides, hydrogen cyanide, organometallic compounds, alcohols, phenols, water etc. The mechanism of Michael addition belongs to the category of nucleophilic additions (Scheme 15; Nu = nucleophile).



Scheme 15

More recently, the scope of the Michael addition has been further extended to intramolecular additions for ring expansion[46].

In this work (55; R = H) was synthesized by reacting the secondary amine (54) with phenyl vinyl ketone (57). This highly reactive Michael acceptor (57) was prepared by the Mannich reaction of dimethylamine hydrochloride, acetophenone, and paraformaldehyde, to form the base (58) followed by quaternisation by iodomethane to give the quaternary salt (59). Hofmann elimination of (59) by potassium carbonate solution afforded phenyl vinyl ketone (Scheme 16).

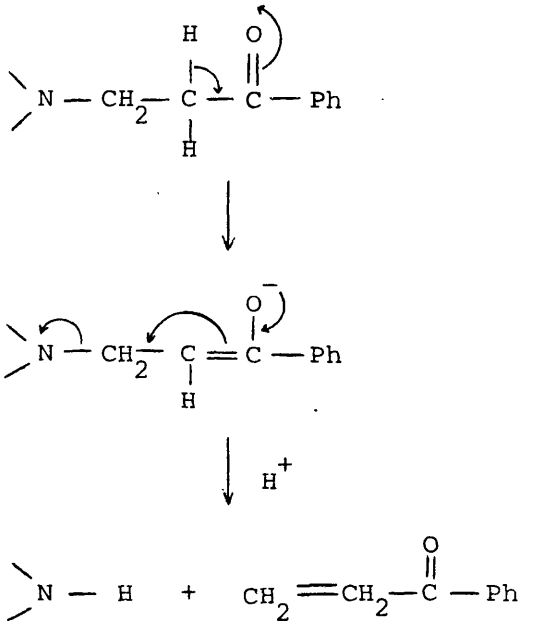


Scheme 16

The yield of the Michael adduct (55; R = H) was over 90%. Direct Mannich reaction of the secondary amine (54) with acetophenone and paraformaldehyde did not proceed to give (55; R = H).

An attempted synthesis of the N-(3-phenyl-3-hydroxypropyl) derivative by reducing (55; R = H) with $NaBH_4$ at room temperature failed because of a reverse Michael reaction[45], as shown by the

appearance of olefinic signals in the ^1H NMR spectrum of reaction product corresponding to those in phenylvinyl ketone. The mechanism of retrograde Michael reaction is the reverse of the Michael addition (Scheme 17), catalysed either by acid or base, or in some cases simply by heating[45].



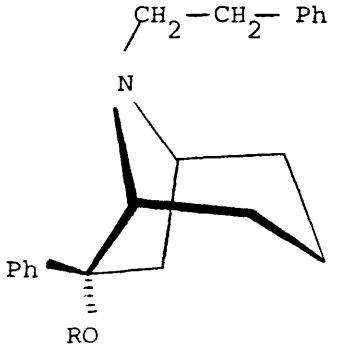
(57)

Scheme 17

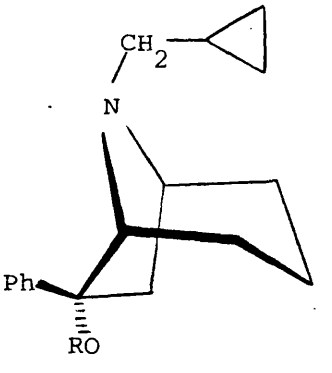
Reaction of the secondary amine (54) with acrylonitrile afforded the Michael adduct (56; R = H) in a 86% yield. The reaction was shown to have completed by t.l.c. and the infrared spectrum showed sharp C ≡ N stretching at 2250 cm^{-1}.

1.2.1.4 Syntheses of N-phenethyl-6β-phenyl-6α-nortropanol (60; R = H), N-cyclopropylmethyl-6β-phenyl-6α-nortropanol (61; R = H), and N-allyl-6β-phenyl-6α-nortropanol (62; R = H), by nucleophilic substitution.

The tertiary alcohols (60; R = H) and (61; R = H) were synthesized by nucleophilic substitution of the secondary amine (54) with phenylacetyl chloride and cyclopropanecarboxylic acid chloride respectively, followed by lithium aluminium hydride reduction of the corresponding amide[1].



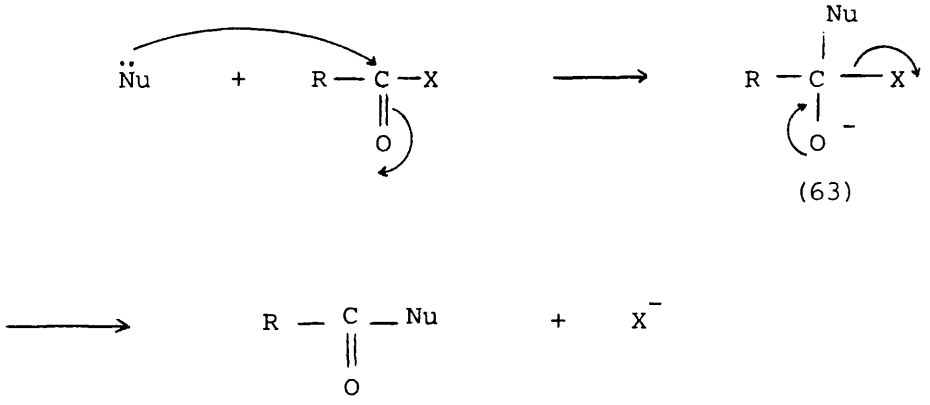
(60)



(61)

Under apolar solvent conditions, nucleophilic substitution at an aliphatic trigonal carbon which is double-bonded to an oxygen, nitrogen or sulphur is considered to proceed via a second order tetrahedral mechanism[47, 48] which is quite different from conventional S_N2 mechanisms. In this tetrahedral mechanism, an intermediate (63) is formed containing the nucleophile, assuming a tetrahedral structure (Scheme 18; Nu = nucleophile, X = halide atom).

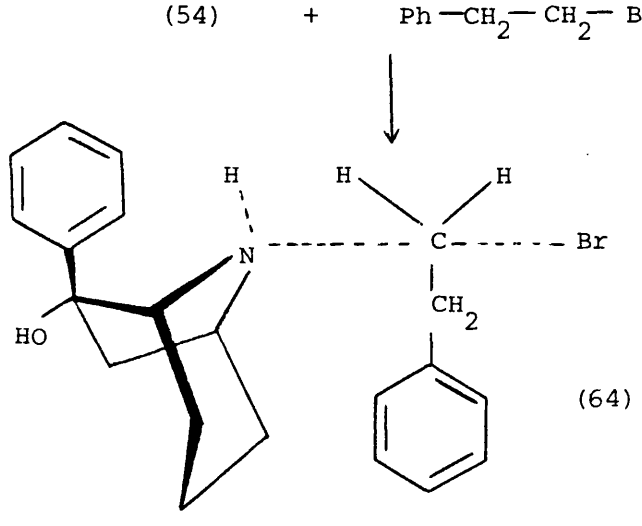
In this work, it was found that the secondary amine (54) did not



(63)

Scheme 18

react with phenethyl bromide to give the tertiary amine (60; R = H) so that the more reactive phenylacetyl chloride was required. This is probably due to certain steric factors which operate during the S_N2 transition state in which the three non-reacting groups and the central carbon must be approximately coplanar[49] (Scheme 19).



(64)

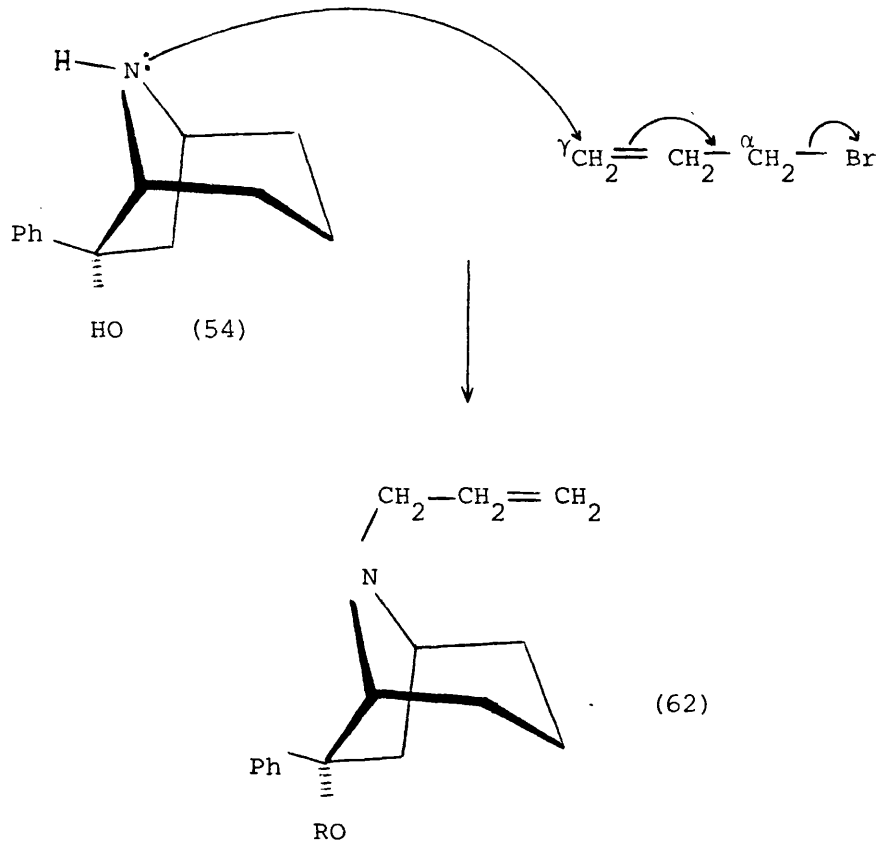
Scheme 19

It is apparent that the enormous steric requirement of the aryl-tropane molecule (54) would generate considerable steric strain in this coplanar pentagonal intermediate (64), and render it unstable in the transition state.

On the other hand, when phenylacetyl chloride is used, the intermediate (63; Scheme 18) assumes a tetrahedral structure with its substituents directed towards the four corners of a tetrahedron. This would help considerably in relieving steric strain in the transition state. In addition, the strong -I inductive effect and planar structure of the carbonyl group in phenylacetyl chloride also promote its reactivity in nucleophilic substitution reactions.

Reaction of the secondary amine (54) with allyl bromide afforded the nortropanol (62; R = H). Owing to possible allylic rearrangements of allyl bromide, the nucleophile (54) may attack the γ-carbon instead of the usual α-carbon via a S_N2' mechanism[50] (Scheme 20).

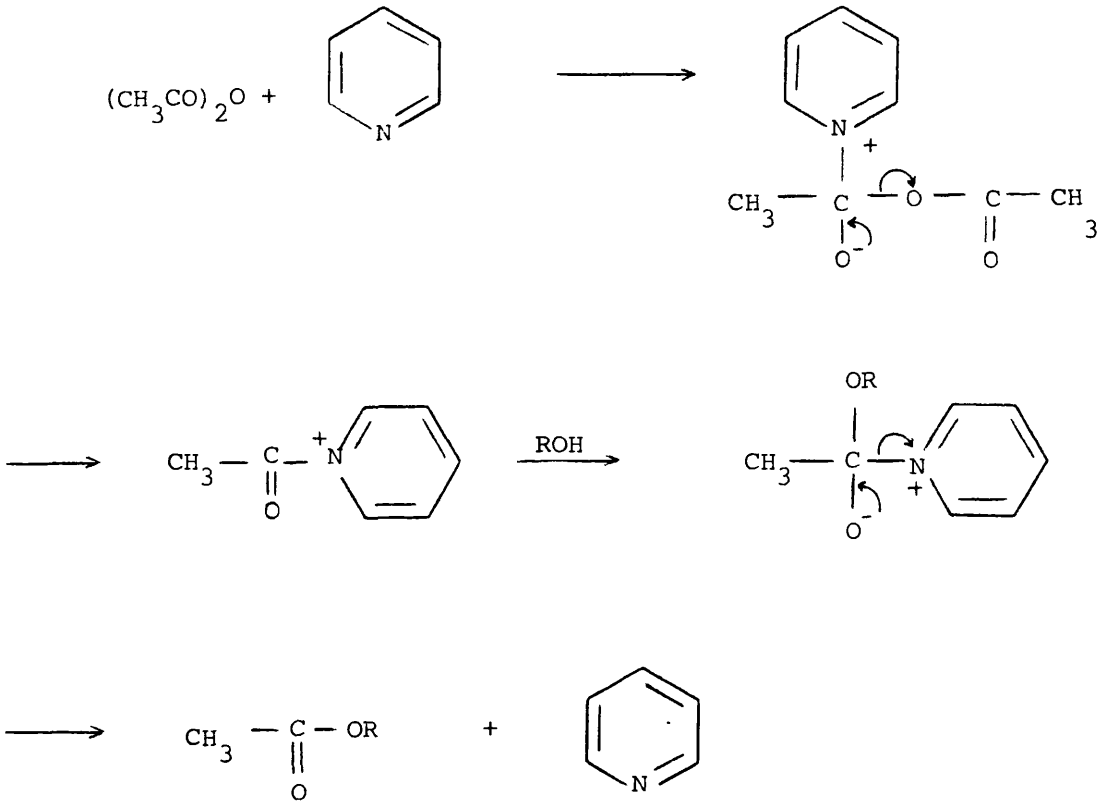
It is suggested that this S_N2' mechanism is appropriate than the conventional S_N2 mechanism when bulky nucleophiles are employed, since the steric hindrance at the γ-carbon is considerably less than that at the α-carbon.



Scheme 20

1.2.1.5 Esterification of the tertiary alcohols of 6β-aryltropanes

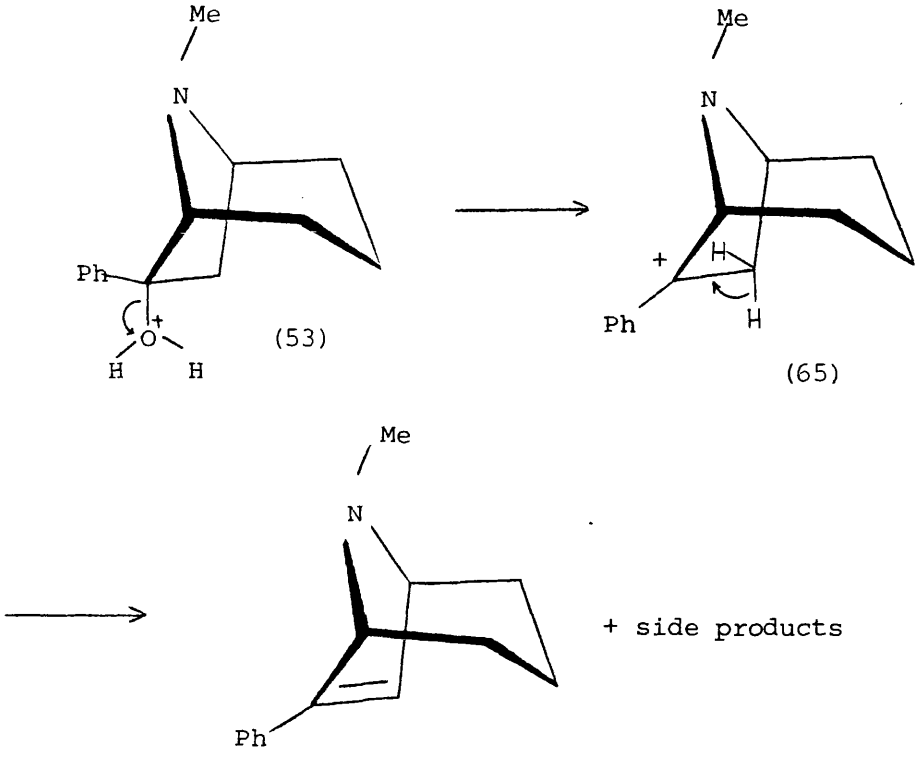
Esterification of tertiary alcohols is considered to be difficult[51, 52]. For example, t-butanol cannot be acetylated by acetyl chloride or acetic anhydride in the presence of pyridine[52]. Some tertiary alcohols, however, can be esterified by propionic anhydride in the presence of pyridine under reflux conditions[53]. The catalysis of the esterification of alcohols by bases is known as nucleophilic catalysis and is considered to involve two successive tetrahedral mechanisms (Scheme 21) [47, 54].



Scheme 21

Early attempts to esterify the tertiary alcohol 6β-phenyl-6α-tropanol (53; R = H) in this work were not successful. Several reported methods which have been successful in esterifying other tertiary alcohols were employed but all resulted in the formation of olefinic and unidentified products. These methods included the use of acetyl chloride with pyridine or triethylamine, propionic anhydride with pyridine[53, 55] or isopropenyl acetate with p-toluene sulphonic acid[56]. The ease of dehydration of (53; R = H) is considered to be the result of the strong electron-releasing effect

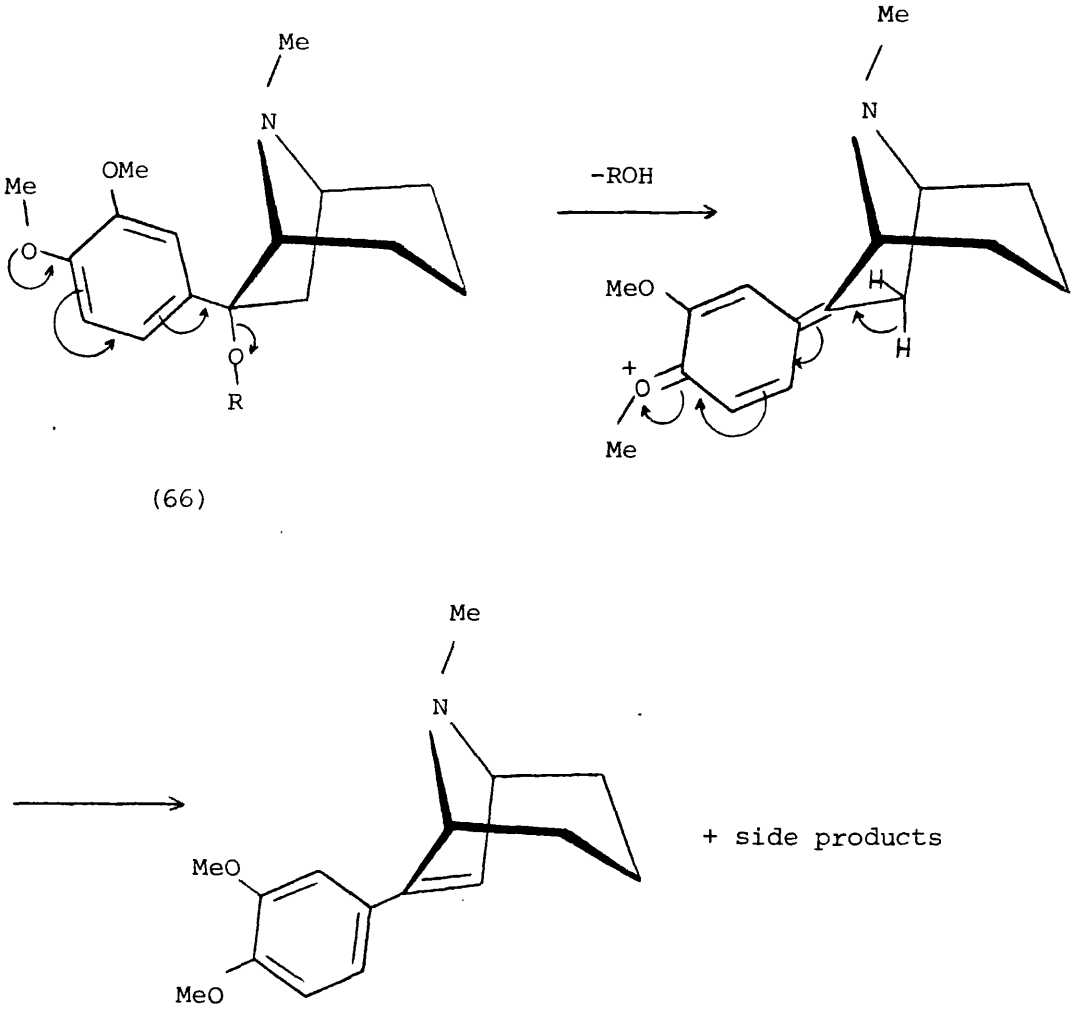
of the 6-phenyl group, which stabilises the intermediate carbonium ion (65; see Scheme 22). In addition, steric hindrance at the C-6 position of (53; R = H) is likely to be an important factor in its resistance to esterification.



Scheme 22

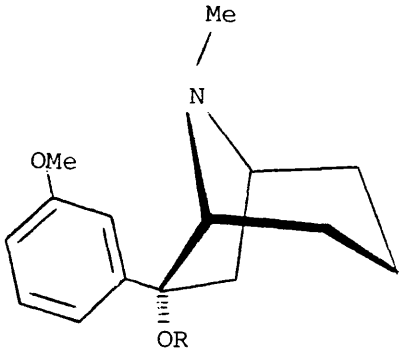
The first successful esterification of (53; R = H) was achieved by heating with acetic anhydride or propionic anhydride in the presence of p-toluenesulphonic acid at 110°C for several days. However, the use of the same method to esterify the 6β-(m,p-dimethyoxyphenyl)-6α-tropanol (66; R = H) resulted in rapid dehydration to give the corresponding olefin accompanied with side products (Scheme 23).

The extreme ease of dehydration of this aryltropanol is probably due to strong +I inductive effect of the aryl O-methyl groups.

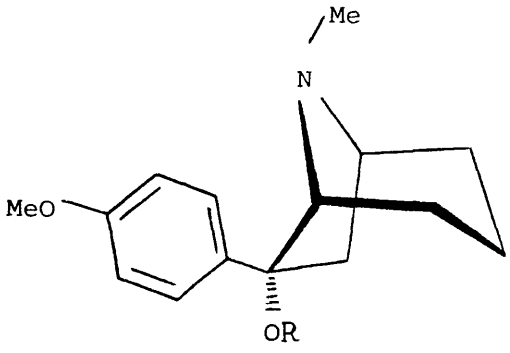


Scheme 23

An attempt to treat (66; R = H) with acetic anhydride in the presence of pyridine also failed to effect esterification. After numerous trial and error attempts, it was found that a modification of the *in situ* method used by Casy and Beckett[57] is very efficient in esterifying the aryltropanols (53), (66; R = H), 67; R = H), and (68; R = H). This facile *in situ* esterification method involved the addition of acetic anhydride or propionic anhydride directly to

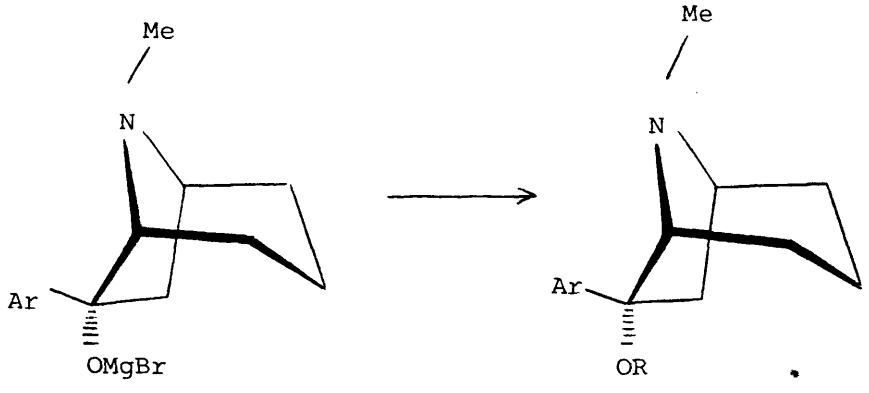


(67)



(68)

the reaction medium after the Grignard reaction was complete (Scheme 24; R = acetyl or propionyl).



Scheme 24

However, this in situ esterification method cannot be applied to the Michael base tertiary alcohols (55; R = H) and (56; R = H) because of the vulnerability of the corresponding N-substituents to Grignard reagents. This problem was solved by employing efficient nucleophilic catalysts such as N,N-dimethylaniline or N,N-dimethyl-4-pyridinamine[58] in the esterification process. The mechanism of

catalysis of these catalysts is suggested to proceed *via* two successive tetrahedral mechanisms as shown in Scheme 21.

An attempted *O*-demethylation of 6β-(*m*-methoxyphenyl)-6α-acetyloxytropanol (67; R = Acetyl) by boron tribromide[83] in room temperature resulted in rapid dehydration to form the corresponding 6-aryl-6-tropene.

1.2.2 Pharmacological results and discussion

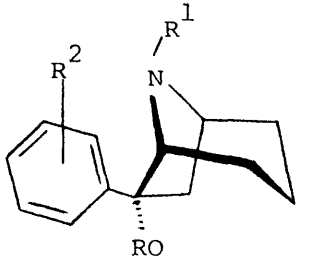
1.2.2.1 Structure-activity relationship considerations.

The analgesic activities of the 6β-aryl-6α-tropanols and their esters were determined by a screening method on guinea-pig terminal ileum[63]. Activities were measured relative to morphine sulphate by studying the effective dose necessary to inhibit normal contraction of the longitudinal muscle of the terminal ileum (Table 2).

As shown in the table, the whole series of 6β-aryltropanols and their esters display very weak morphine-like agonist activity on guinea-pig ileum. The agonist activities of all these tropanes except (53; R = acetyl) were not reversed by naloxone, showing that these drugs may not exert their action by interacting directly with the opiate receptor. The potential antagonists were found to be either inactive (62), or weakly active (61), (see Table 2).

The apparent weak analgesic activity of this 6β-aryltropanol series demand close consideration of the structure of the molecule and the structure-activity relationships of closely related analgesics,

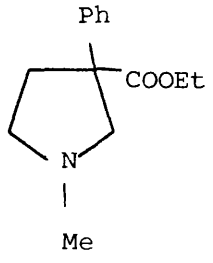
Compound No.	R	R^1	R^2	Agonist Activity (I.D./μg ml^{-1})	Antagonist Activity (I.D./μg ml^{-1})	Reversibility by Naloxone
53	CH_3CO-	$-CH_3$	H	5	-	+ (partially)
53	C_2H_5CO-	$-CH_3$	H	1	-	-
67	H	$-CH_3$	$-OCH_3$ (m)	40	-	-
67	CH_3CO-	$-CH_3$	$-OCH_3$ (m)			
68	H	$-CH_3$	$-OCH_3$ (p)			
68	CH_3CO-	$-CH_3$	$-OCH_3$ (p)	-	-	
66	H	$-CH_3$	$-OCH_3$ (p,m)			
66	CH_3CO-	$-CH_3$	$-OCH_3$ (p,m)	-	>10	-
55	CH_3CO-	$-CH_2CH_2COPh$	H	>10	>10	-
56	H	$-CH_2CH_2CN$	H	-	-	
56	CH_3CO-	$-CH_2CH_2CN$	H	-	-	
60	CH_3CO-	$-CH_2CH_2Ph$	H	>10	-	-
62	CH_3CO-	$-CH_2-CH=CH_2$	H	>10	-	-
62	H	$-CH_2-CH=CH_2$	H	-	-	-
61	CH_3CO-	$-CH_2$-cyclopropyl	H	-	10	



Morphine sulphate ($I.D._{50}$ 6.5 ng ml^{-1})

Table 2. Analgesic activities of 6β-aryl-6α-nortropanols on guinea-pig ileum

Pyrrolidine analogues of pethidine have been synthesized and evaluated. The first member of this series (69)[64] was found to be inactive and so were related compounds[65]. However, the pyrrolidine derivative, prodilidene (70), is only slightly less potent than pethidine and has received intensive biological evaluation[66].



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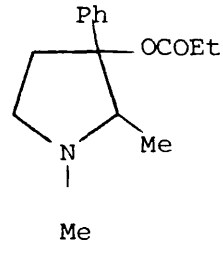
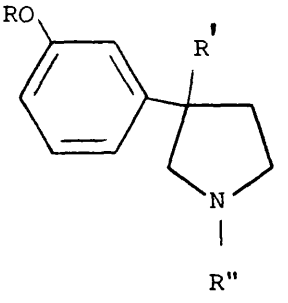


(70)

Various pyrrolidine derivatives with general structure (71) were synthesized and tested for analgesic activity (Table 3). One of these compounds, known as profadol (71; R = H, R' = Pr^n, R" = Me), was found to be 2.5 times as active as codeine on the rat tail squeak test[67-70]. The enantiomers of profadol were separated. The (-)-enantiomer was found to be about twice as active as the (+)-enantiomer. It was found that Pr^n is not actually an optimal substituent at the 3 position, substitution with 3-$CHMe_2$, 3-CH_2CHMe_2, or 3-CH_2CMe_3 giving compounds with higher potency as well as lower toxicity than profadol itself[70]. However, substitution at the 3-position with smaller alkyl groups such as methyl or ethyl groups, decreases the potency. Replacement of phenethyl for methyl on the nitrogen of profadol increased potency and decreased toxicity[70]. However, replacement of the N-methyl group with N-Pr^n gave a compound which was inactive in the rat tail pressure test. Of interest, further increase in the chain length of the

Table 3.[70,71] Relative analgesic potencies of profadol and its analogues

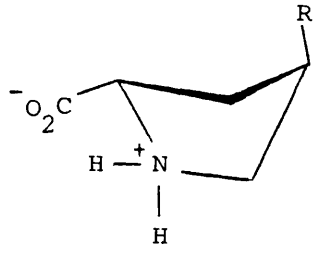


(71; R = H)

R'	R"	Relative Potency (Codeine = 1.0)
$(CH_2)_2Me$	Me	2.5
Et	Me	1.0
Me	Me	0.2
$CHMe_2$	Me	3.0
CH_2CHMe_2	Me	2.7
CH_2CMe_3	Me	3.8
COOEt	Me	0.4
$(CH_2)_2Me$	$(CH_2)_2C_6H_4$-p-OH	3.5
$(CH_2)_2Me$	$(CH_2)_2C_6H_4$-p-NH_2	5.8
$(CH_2)_2Me$	H	None
$(CH_2)_2Me$	$(CH_2)_2Me$	None
$(CH_2)_2Me$	$(CH_2)_3Me$	0.8
$(CH_2)_2Me$	$(CH_2)_4Me$	1.5
$(CH_2)_2$	$(CH_2)_5Me$	1.1

N-alkyl group(e.g. Bu^n) afforded compounds displaying some analgesic activity (see Table 3)[71].

Configurational and conformational studies of these pyrrolidine analgesics have not been reported. However, it is suggested that these pyrrolidine derivatives, like pyrrolidine[72] itself, may exist in a puckered ring and may undergo pseudorotation. Prodilidene (70) and its derivatives have certain structural resemblances to trans-4-hydroxy-L-proline (72) which was determined by ^{1}H NMR studies[73] to be strongly puckered. Therefore, (70) and its derivatives may also assume a conformation very similar to (72).



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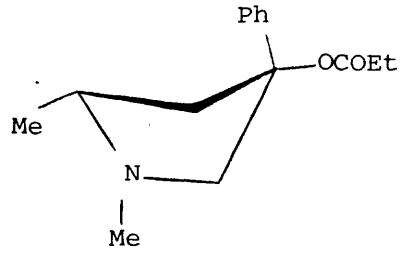
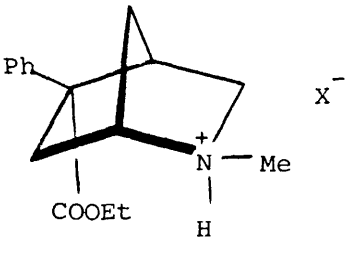


(70)

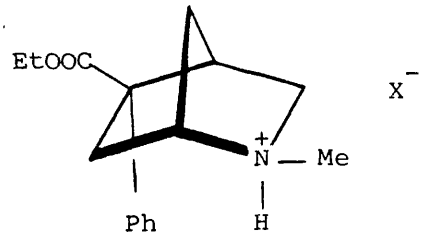
An important point which emerged from the structure-activity studies of the pyrrolidine analgesics is that slight variation in the hydrophobic part of the molecule causes marked variation in analgesic activity. It is likely that certain stereospecific hydrophobic interactions are essential for triggering the response at the opiate receptor. Besides, it is suggested that the multiplicity of the opiate receptors may be the most reasonable explanation for the non-linear structure-activity relationships in variation of the N-substituents of profadol (Table 3). No data for 2,5-dialkyl-, or 2,4-dialkyl-3-acyloxy-3-phenylpyrrolidines are reported.

The 3-substituted aryltropane analogues of pethidine (41; R = Et)[14], (47)[15], and (48)[16] all have potencies slightly greater or equivalent to pethidine. Thus, it appears that the relative configuration of the phenyl ring is not a very important criterion for analgesic activity.

Portoghese et al.[74] synthesized a pair of diastereoisomeric conformationally rigid pethidine analogues (73) and (74) and found that (74) was six times more potent than (73) and twice as potent as pethidine. The interatomic distance between the centre of the phenyl ring and the nitrogen atom is about 6 Å and 4 Å for (73) and (74) respectively. Thus, it appears that the interatomic distance between the aryl ring and the nitrogen atom in the drug molecule is another important factor in eliciting morphine-like response. However, because a factor of 3 or 4 in potency is not great when one considers the large difference in molecular geometry of these molecules (73) and (74), Portoghese et al.[74] rationalised the minimal conformational requirements for analgesic activity in terms of differing modes of interaction with the receptor.

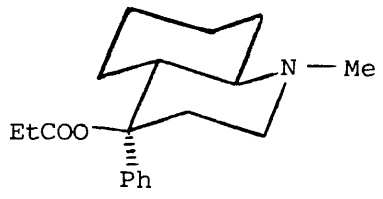


(73)

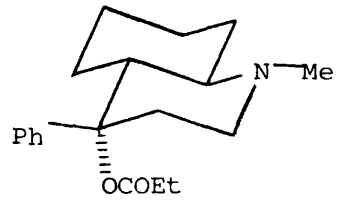


(74)

Smissman and Steinman[75] synthesized two epimeric, conformationally restricted prodine analogues (75) and (76) and found them to be equipotent. As a result, it was suggested[75] that no definite conformational requirement for the phenyl group is required for analgesic activity.

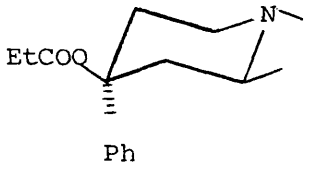


(75)



(76)

On the other hand, the orientation of hydrophobic groups in the molecule markedly affects its potency. The 4α-phenyl piperidine analgesic (77)[76] is more than three times as potent as pethidine while (78)[77] and (79)[78] are inactive.



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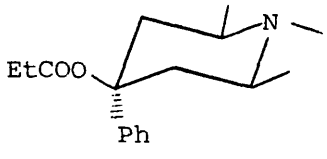

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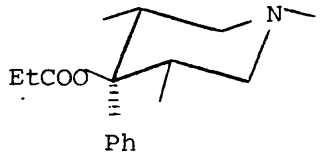


(79)

In the 6β-aryltropanol series of analgesics, the most active member is (53; R = Et), but even for this compound the potency is only 0.0065 times that of morphine. Substitution of methoxy groups for hydrogen in the aryl ring or phenylalkyl groups for methyl

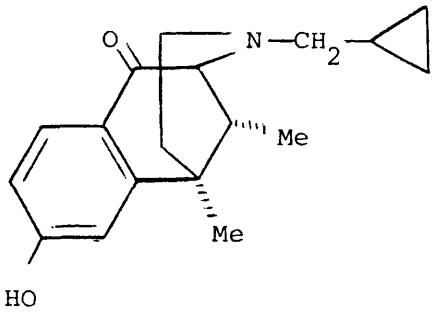
groups in the ring nitrogen result in weaker activities (Table 1). The N-allyl derivative (62; R = acetyl) is devoid of antagonistic activity whereas the N-cyclopropylmethyl derivative (61; R = acetyl) is a very weak antagonist of morphine and also a weak agonist itself. The author envisages the critical importance of spatial orientation of the hydrophobic groups in potential analgesic molecules. These groups must be accommodated by certain hydrophobic pockets[81] in which non-bonded interactions may operate to trigger the response of analgesia. It is further suggested that the molecular bulk of the molecule as a whole is not as important as the orientation of its non-polar groups. Certain opiate receptors must be available for the accommodation of molecules with very high molecular weight like the potent endogenous opoid peptides[88, 89, 92, 99].

The weak affinity of the 6β-aryltropanes for the opiate receptor is attributed to the operation of steric hindrance, probably conferred by the propyl bridge of six-membered ring of the tropane. Alternatively, lack of hydrophobic groups in the C-1, C-5 or C-2, C-4 position may render the molecule unable to bind to the hydrophobic pockets[81] of the opiate receptors necessary to trigger the analgesic response. Of interest, the 6α-phenyltropane (120) synthesized in this work (see Part 3) is devoid of analgesic action in guinea pig ileum, but is fairly potent (500 ng ml^{-1}; about 1/5 of the potency of morphine) in mouse upper duodenum. This finding strongly supports the theory of multiple opiate receptors[79, 80, 82] and may also indicate that α-aryl configuration in the 6-aryltropane series may be more favourable for binding to certain opiate receptors.

It is suggested that for future work, the synthesis of 6α-aryl-6β-tropanols and the corresponding esters are necessary since the α-orientated aryl group may be crucial for potent activity. In addition, verification or otherwise of the hydrophobic pocket[81] hypothesis and the multiple receptor theory may be aided by incorporation of alkyl groups with different chain lengths to either the C-2, C-4, C-3, C-6 or C-7 positions, followed by pharmacological evaluation of the resulting compounds.

1.2.2.2 The multiplicity of the opiate receptor

The paradoxical structure-activity relationships of synthetic morphine-like analgesics cannot be explained by the existence of a single opiate receptor. The presence of a limited number of receptors with different stereoselectivity of ligands is most probable. Martin[79, 80] has identified the existence of three different opiate receptors: morphine (46) is the prototype agonist for the μ receptor, ketocyclazocine (80) for the k-receptor and SKF-10047 (81; the N-allyl analogue of normetazocine) for the σ receptor. This hypothesis of multiple receptors is based on suppression and precipitation studies of morphine and cyclazocine-dependent chronic spinal dogs. In addition, Martin[80] suggested that cyclazocine appears to have both k and σ agonistic activity but no activity at the μ-receptor; morphine may have both μ and k activity; and nalorphine is a partial agonist of the k type.[80] Pentazocine is suggested to be an agonist of the k and σ type, having a lower affinity for the σ receptor than the k receptor.[82]



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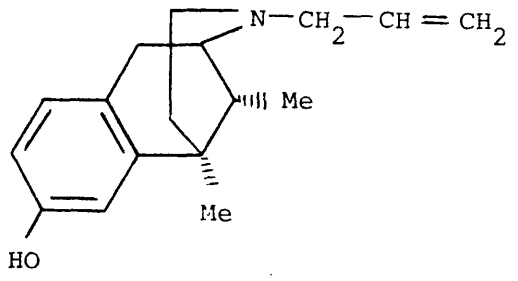


(81)

Thus, the difference in potency of synthetic narcotic analgesics an be rationalised by the degree of complementarity they express to the different opiate receptors. The existence of several receptors can also explain the high stereospecific requirement of the receptors as well as the presence of a vast number of potent agonists with a wide range of structures.

Feinberg et al.[86] suggests that the phenyl ring A and the amino nitrogen of the drug molecule are crucial for all opiate actions, and that a further ring F is essential in potent agonists like phenazocine (82) and the 6,14-endoethenotetrahydrothebaine derivative (PET; 83).

The model of Feinberg et al.provides some explanation for the fact that by substituting allyl, cyclopropylmethyl or cyclobutylmethyl groups to the basic centre, the agonist molecule is converted to an antagonist one. In addition, this model also explains the action of nalorphine, which is a mixed agonist-antagonist. However, this

model cannot satisfactorily explain the fact that introduction of 'antagonistic' N-substituents like allyl, cyclopropylmethyl groups into the 4-phenylpiperidine series[12] and the phenylmorphans[87] afford agonists instead of antagonists.

An alternate approach for the explanation of the paradoxical structure-activity relationship of synthetic opiates is the hypothesis of multiple modes of interaction between ligands and opiate receptors proposed by Portoghese[98]. This hypothesis envisages the association of different ligands with different recognition loci on the receptors, the outcome of which is the divergent stereochemical requirements for different opiates.

Other hypotheses have been proposed. Belleau[103] proposed the clastic binding theory, suggesting that the nitrogen lone pair of the analgesic molecule may interact with an electrophilic site, whereupon a stereospecific electron transfer to the opiate receptor forms part of the overall receptor response. However, this hypothesis remains controversial[100].

As a whole, Martin's hypothesis of the existence of multiple receptors[79, 80, 82] appears most useful in explaining the paradoxical structure-activity relationships of synthetic opiates, whereas the several hypothetical models of Feinberg et al., Portoghese and Belleau are also feasible. Of course, the opiate receptors are not designed endogenously for interacting with synthetic morphine-like compounds, but for various naturally occurring endogenous peptides

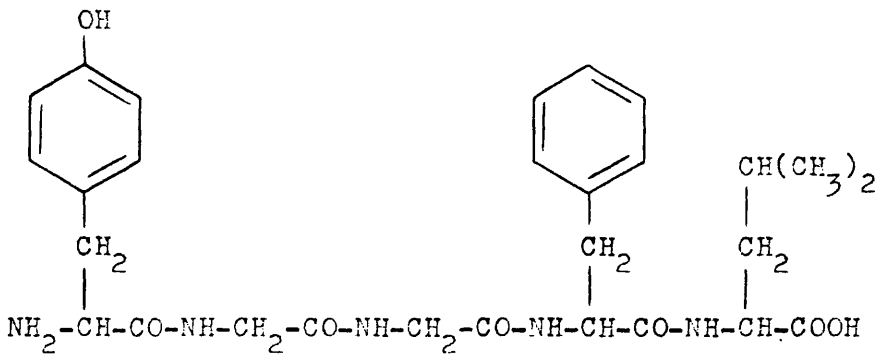
known as enkephalins[88, 89], and endorphins[92] which have potent analgesic activities reversible by naloxone.

Enkephalins are a pair of pentapeptides, H-Tyr-Gly-Gly-Phe-Met-OH (Met^5-enkephalin) and H-Tyr-Gly-Gly-Phe-Leu-OH (Leu^5-enkephalin). Endorphins are the pituitary hormone β-lipotropin (β-LPH) related opoid peptides. The whole C-terminal portion of β-LPH (a.a. residues 61-91) is known as β-endorphin which has potent analgesic effects[92]. Two pituitary peptides, β-LPH (a.a. residues 61-76) known as α-endorphin and γ-endorphin, β-LPH (a.a. residues 61-77) were also isolated. A novel pituitary endorphin known as dynorphin[99], consisting of 14 - 15 amino acid residues was isolated and reported to be 700 times more potent than Leu^5-enkephalin on guinea pig ileum preparations. A peptide called substance P[95] may mediate the process of analgesia as the primary noiceptive neurotransmitter. In addition, it has been suggested that enkephalins may be involved in the process of analgesia during acupuncture[93] and electrical stimulation[94]. The recent discoveries of these endogenous opoid peptides also prove the correctness of Martin's prediction in 1967[90]: "morphine-like compounds might mimic an ongoing biochemical process."

Intensive investigations have been carried out on conformational aspects of Leu^5-enkephalin (84). X-ray crystallographic studies[97] of this pentapeptide indicate that two intramolecular hydrogen-bonds exist between the amino nitrogen of tyrosine and the carbonyl oxygen of phenylalanine, as well as between the nitrogen atom of phenylalanine and the carbonyl oxygen of tyrosine. These intra-

molecular hydrogen bonds in turn cause the peptide chain to assume a β-bend conformation in the sequence Tyr-Gly-Gly-Phe (Fig. 7).

Attempts[97, 98] have been made to correlate the structure of morphine and its congeners with that of enkephalin. It was suggested[97] that the orientation of the phenolic ring A of morphine corresponds to the phenolic ring A of the tyrosine residue of Leu^5-enkephalin, and that the orientation of the oxygen atom of the 6-hydroxy group and the amino nitrogen of morphine correspond to the leucine carboxyl oxygen and tyrosine amino nitrogen of Leu^5-enkephalin respectively. A hydrophobic region constituted by the C-7 and C-8 face of morphine corresponds to the leucine side chain in Leu^5-enkephalin or to the methionine side chain in Met^5-enkephalin. The phenyl ring F of potent opiates such as phenazocine may correspond to the phenyl ring of phenylalanine in enkephalins (Fig. 8).



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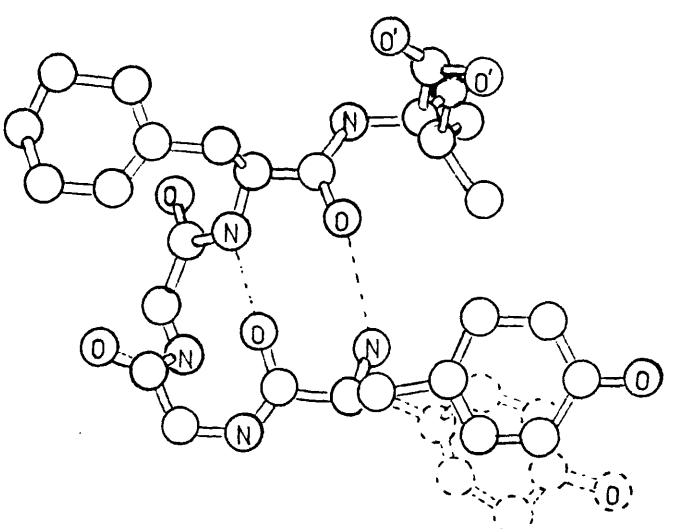
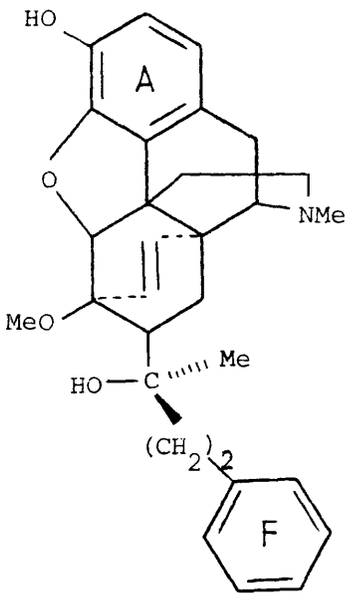


Fig. 7. Conformation of Leu^5 enkephalin showing intramolecular hydrogen bonds and β-bond[97]. Dashed lines between nitrogen and oxygen atoms are hydrogen bonds; dashed lines of the Tyr side chain represent the second conformation of the phenolic ring.



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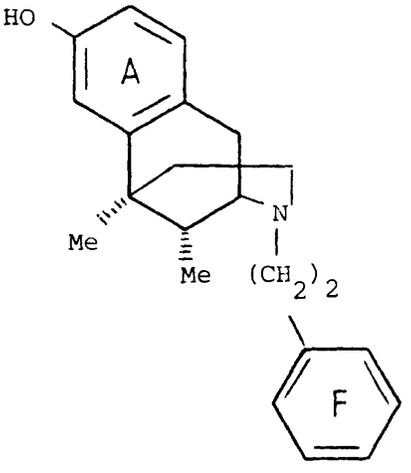

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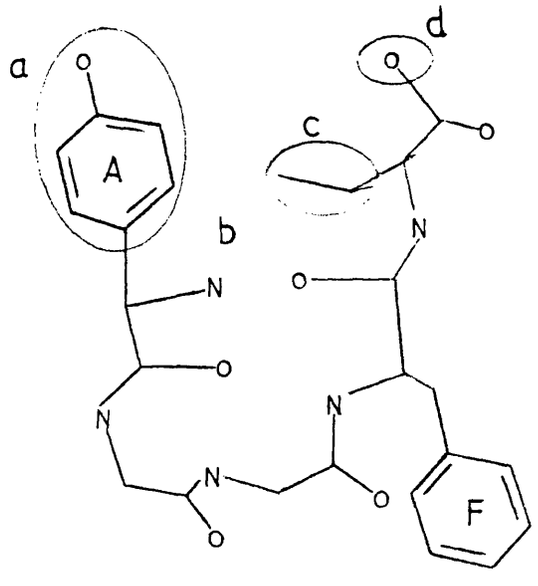

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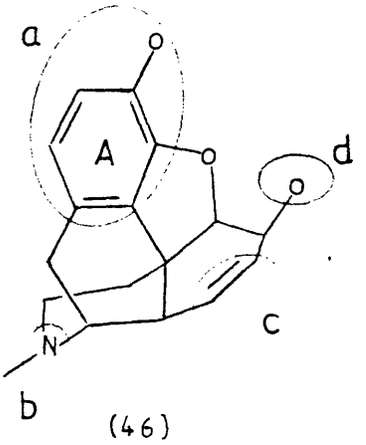

(46)

Fig. 8. Stick drawings from crystallographic coordinates of Leu^5 enkephalin (84) and morphine (46) showing analogous regions.

A striking feature of the structure of endogenous opoid peptides is their unusual steric requirement which is much greater than that of known synthetic opiates. This may indicate that the opiate receptors are composed of oligomeric subunits arranged in a three dimensional topography. Complex biochemical processes may be involved in inter-relating these subunits.

Binding studies[83,84,101] of ^{3}H -etorphine and ^{3}H -naltrexone in rat brain suggests that the binding of opiates to the receptor exhibits positive cooperativity, indicating the possibility of oligomeric structures In addition, in the presence of sodium ions the binding sites have greater affinity towards antagonists and lower affinity towards agonists[84, 85]. Sodium ions also help in the protection of receptors against inactivation of their SH groups[102], suggesting that Na^{+} causes alteration in the orientation of these SH groups, rendering them less accessible to inactivation by SH^{-} blocking agents such as N-ethylmaleimide.

It was suggested[63, 101, 102] that both agonist and antagonist bind to the same receptor which can exist in at least two conformations allosterically modulated by sodium ions. Since the fluid bathing the cellular membranes of the brain is rich in sodium ions it was suggested that the opiate receptor normally exists in the sodium-binding antagonist state, with considerably greater affinity for antagonists than corresponding agonists. In the sodium-free state a given agonist and a corresponding antagonist can bind to the receptor with about equal affinity.

It is quite apparent that the present knowledge of the actual three-dimensional structure and biochemical nature of the opiate receptors, is still at its rudimentary stage. The genuine stereochemical features of the receptors would probably await the isolation of intact receptors followed by direct examination by X-ray crystallographic methods.

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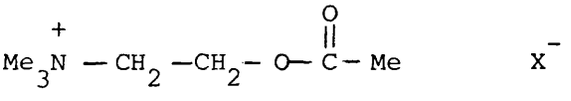
Part 2. Some potential cholinergic agonists based on 6-substituted tropanes.

2.1 Introduction

The dual pharmacological actions of acetylcholine (85; X^- = Br^-, Cl^-) were established by the classical experiments of Dale[1]. They are of two categories - those physiological actions of acetylcholine miniced by (+)-muscarine (86; 2S, 3R, 5S) and S(-)-nicotine (87) are called the muscarinic and nicotinic actions of acetylcholine respectively.



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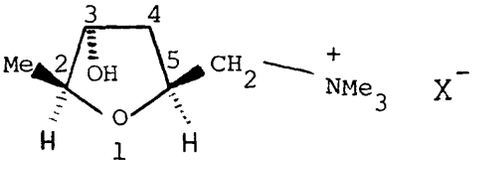

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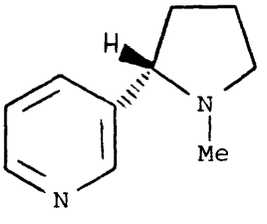

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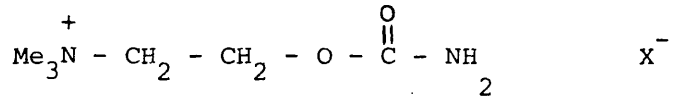
The fact that acetylcholine is hydrolysed rapidly by acetylcholinesterase and thus cannot be used as an efficient therapeutic agent has promoted intensive research into the synthesis and pharmacological evaluation of mimics of acetylcholine. Examination of the structure-activity relationships of these mimics in turn provide information of the chemical and stereochemical requirements for cholinergic activity.

The trimethylammonium group of acetylcholine appears to be

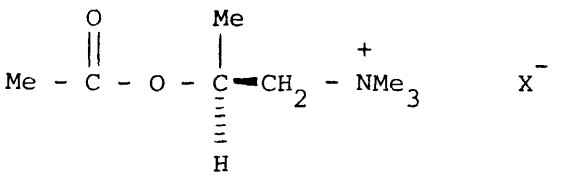
optimal in cholinergic agonists and replacement by hydrogen atoms abolishes nicotinic activities and retains only very weak muscarinic actions[2]. Substitution of more than one N-methyl group by ethyl groups causes a successive decrease in potency[3].

Replacement of the acetyl group of acetylcholine by higher acyl groups produced less potent analogues, some of which have physiological activities[4,5] different from that of acetylcholine. Substitution of the acetyl group by a carbamyl group produces the interesting compound carbachol (88), with greater nicotinic activity and retention of muscarinic action[6, 7].



(88)

The distance between the quaternary nitrogen and the ester function of acetylcholine appears to be critical. Attempts to replace the ethylene bridge by higher alkyl groups result in marked decrease in potency[8]. However, addition of a methyl group β to the quaternary nitrogen atom afforded acetyl-β-methylcholine, the S(+) enantiomer (89)[9, 10] of which has muscarinic activity 20 times more potent than acetylcholine (but much weaker nicotinic activity). Replacement of the β-methyl group of (89) by higher alkyl groups such as propyl or butyl groups markedly decreases the potency.



(89)

Schueler[11] suggested that "the flexibility of acetylcholine molecule is an important attribute to be considered in collating structure with pharmacological activity". X-ray crystallographic studies by Sorüm [12] further confirmed that acetylcholine exists in two conformations, the extended or transoid conformation and the "ring" or cisoid conformation (Fig. 9). Sorüm suggested that these conformations may account, in some unspecified way, for some of its pharmacological activities. Archer et al.[17] considered that the muscarinic properties of acetylcholine are associated with the transoid conformation and the nicotinic actions are associated with the "ring" or cisoid conformation.

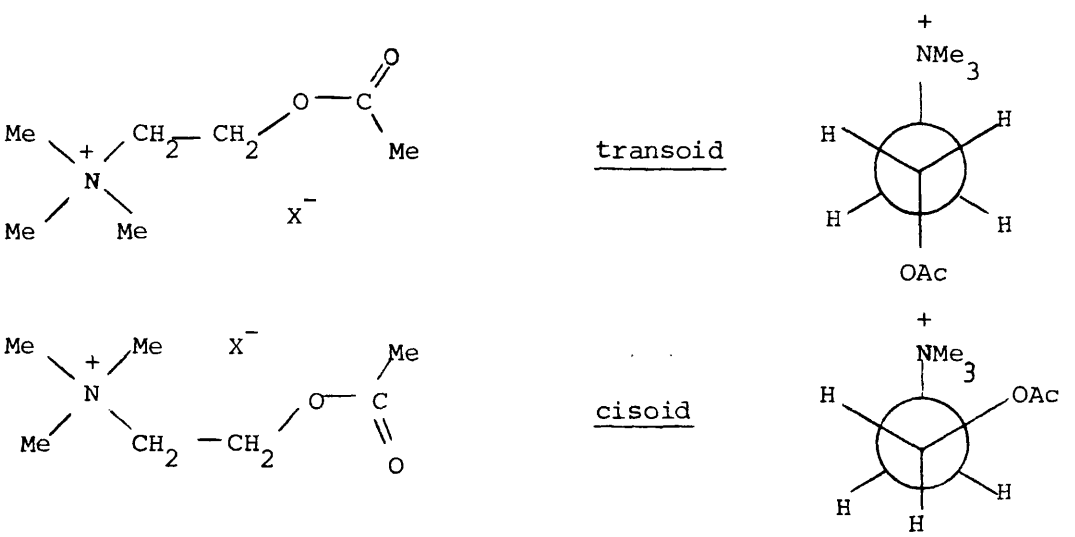


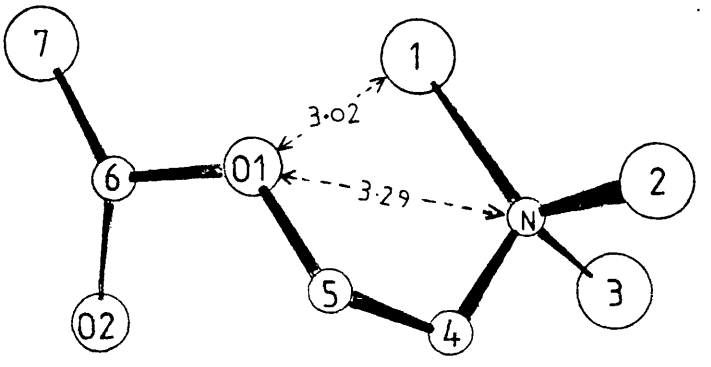
Fig. 9

Solid-state X-ray crystallographic studies[13] of acetylcholine and muscarine indicated striking similarities in conformational preference. Muscarine iodide was found to assume a quasi-ring conformation resembling that of acetylcholine bromide (Fig. 10a). It has been suggested that the stabilizing factor for this higher energy conformation is the electrostatic interaction between the charged nitrogen group and the ether oxygen of these molecules. The interatomic distance between the quaternary nitrogen and ether oxygen in acetylcholine and muscarine are also similar (see Fig. 10a) and the indication is that the anionic centre and the esteratic centre is separated by about 3 Å.

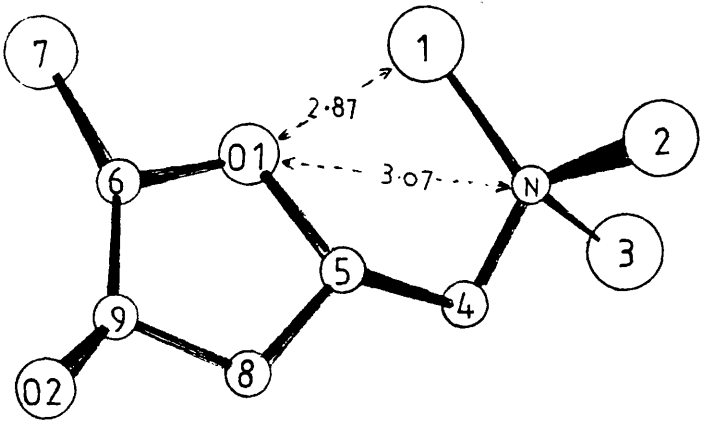
From X-ray crystallographic studies, the conformational requirements of acetylcholine and its congeners were suggested[14] to be defined by the four torsion angles (Fig. 10 b).

Of these four torsion angles $\tau 2$ and $\tau 3$ are of crucial importance because these parameters define the stereochemical relationships between critical moieties such as the quaternary nitrogen and the esteratic oxygen, and between the esteratic function and the ethylene bridge. The value of $\tau 2$ and $\tau 3$ in most cases fall in the range of $+73^{\circ}$ to $+137^{\circ}$, and $180^{\circ} \pm 35^{\circ}$ respectively[14].

Based on X-ray crystallographic work of Pauling *et al.*[14], Chothia[15] explained the dual pharmacological actions of acetylcholine by assuming that acetylcholine and its mimics are reactive at the muscarinic receptor with the methyl side of the molecule



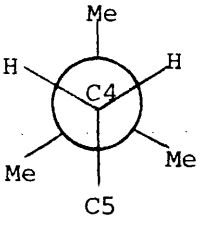
(85)



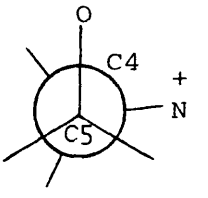
(86)

Fig. 10a The structure of the acetylcholine molecule (85) in crystals of acetylcholine bromide and the structure of the muscarine molecule (86) in crystals of muscarine iodide. Interatomic distances (Å) are shown.

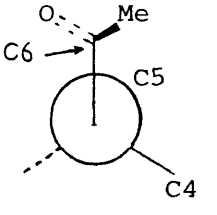
τ 1 C5 - C4 - N - C3



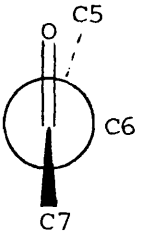
τ 2 O1 - C5 - C4 - N

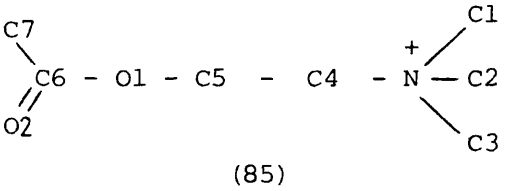


τ 3 C6 - O1 - C5 -C4



τ 4 C7 - C6 - O1 - C5

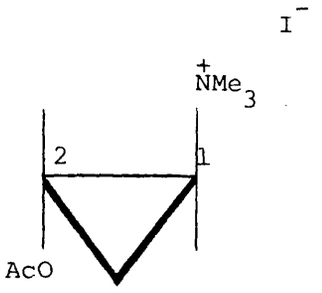




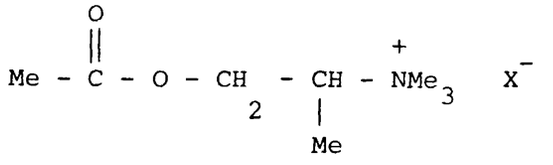
(85)

Fig. 10b

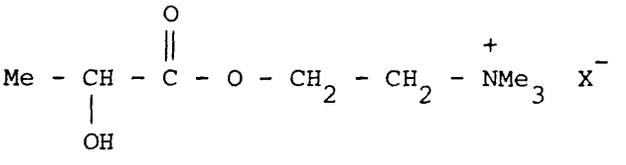
when the carbonyl side is blocked. For example S(+)-acetyl-β-methylcholine; (89), S(+)-trans-2-acetyloxycyclopropyltrimethylammonium iodide (ACTM; 90), and muscarine (86), (Fig. 11). Similarly, he suggested that acetylcholine and its mimics are reactive at the nicotinic receptor with the carbonyl side of the molecule when the methyl side is blocked. For example R(+)-acetyl-α-methylcholine (91) and lactoylcholine (92), (see Fig. 11 and Fig. 12).



(90)



(91)



(92)

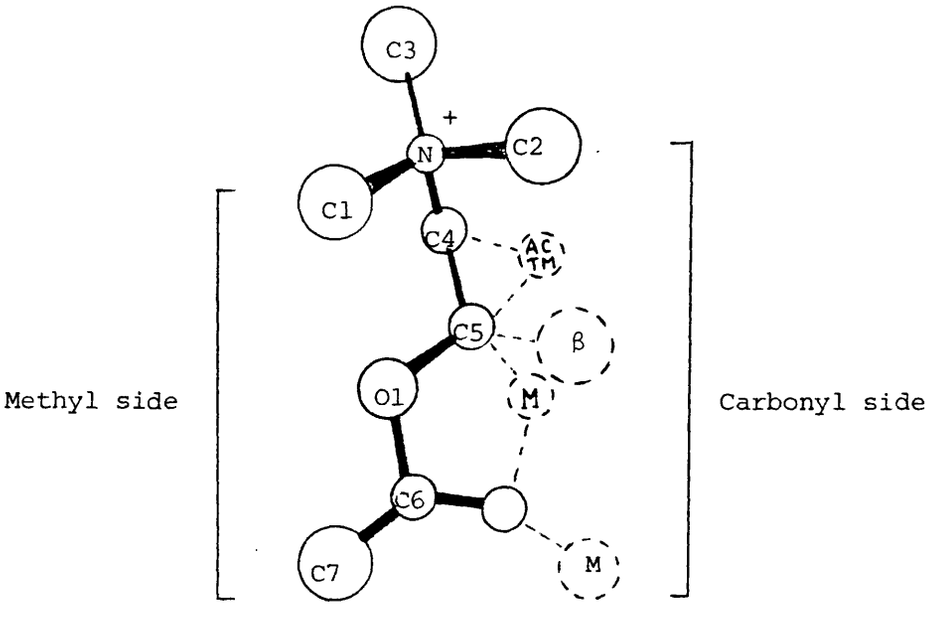
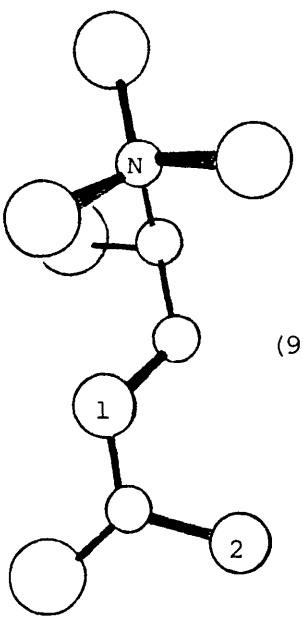
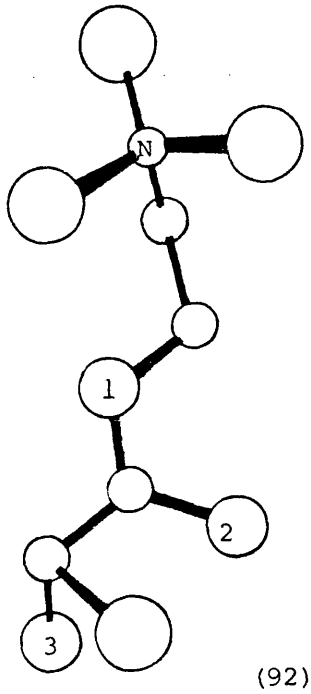


Fig. 11. (The atoms belonging to (90) are labelled ACTM; to (89) as β; to (86) as M)



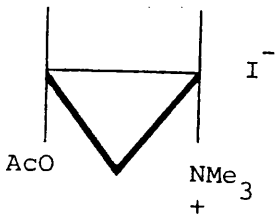
(91)



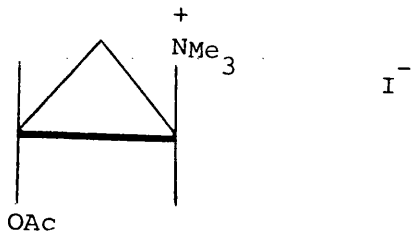
(92)

Fig. 12

To verify the hypothesis of Archer et al.[17] which stated that the transoid and cisoid conformation of the acetylcholine are associated with muscarinic and nicotinic activities, respectively, rigid acetylcholine mimics with "frozen" configurations at the carbons bearing the quaternary nitrogen and ester functions were prepared and pharmacologically evaluated. The most significant of these synthetic rigid acetylcholine mimics is the ACTM series[18,19]. The S(+)-trans ACTM (90) has slightly higher muscarinic activity than acetylcholine in certain test systems and it is several hundred times more active than R(-)-trans ACTM (94). (±)-cis ACTM (93) is virtually inactive.



(93)



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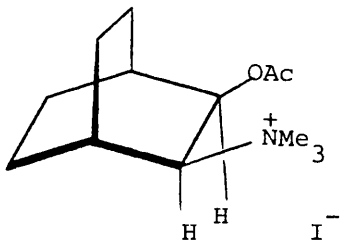
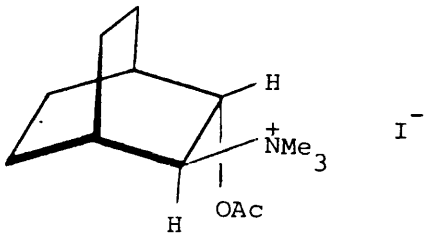
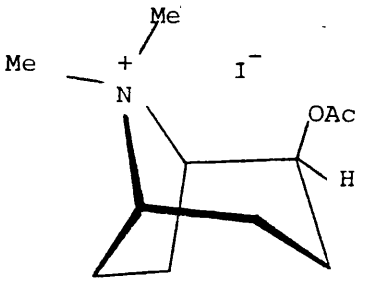


(95)



(96)



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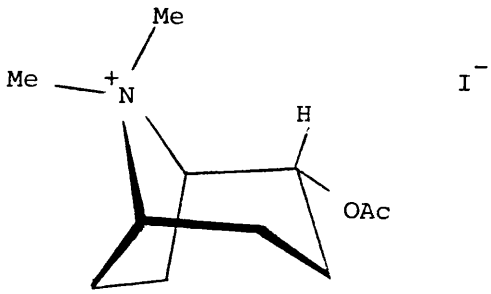
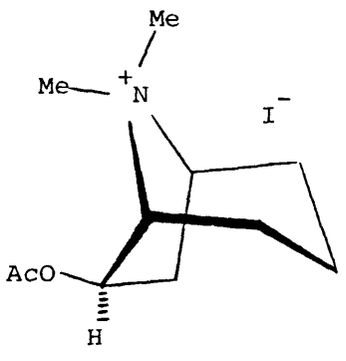


(97)

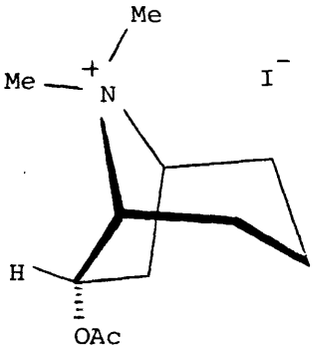
Some other rigid mimics of acetylcholine were prepared, but most of them have much weaker actions than acetylcholine. Trans-3-trimethylammonium-2-acetyloxybicyclo[2,2,2]octane iodide (96) is a weak muscarinic agonist whereas its corresponding cis-isomer (95) is inactive[20, 21].

Rigid cholinergic agonists based on 2-substituted tropanes were synthesized[16,17]. 2α-acetyloxytropane methiodide (97) is a weak muscarinic agonist on isolated rat sigmoid colon whereas 2β-acetyloxytropane methiode (98) is virtually inactive.

The 5-membered pyrrolidine ring of the tropane ring also offers a rigid frame-work to prepare rigid acetylcholine mimics. The racemates (±)-6β-acetyloxytropane methiodide (99) and its diastereoisomer (±)-6α-acetyloxytropane methiodide (100) have been prepared in previous work[25]. However, the pharmacological activities were not evaluated until recently (see Section 2.2.4). The emphasis of the work in Part 2 has been laid on the resolution of (±)-6β-tropanol (51) and the preparation of the enantiomers, (+)-6β-acetyloxytropane methiodide and (-)-6β-acetyloxytropane methiodide (Section 2.2.3).



(99)



(100)

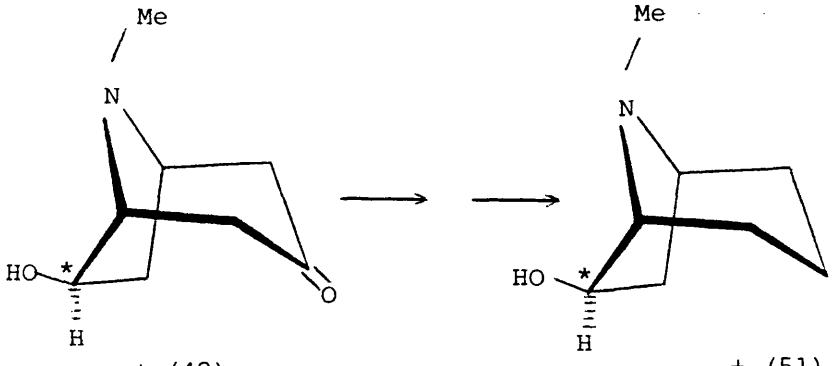
2.2 Discussion

2.2.1 General scheme of synthesis

The synthetic route starts from the Wolff-Kishner reduction of (±)-6β-hydroxytropinone (49) to afford (±)-6β-tropanol (51). Resolution of (±)-6β-tropanol gave the enantiomers (+)-6β-tropanol and (-)-6β-tropanol. Esterification of each enantiomer with acetic anhydride at room temperature generated the corresponding (+)-acetyloxytropane and (-)-acetyloxytropane. Quaternisation of each enantiotopic acetate with methyl iodide gave (+)-6β-acetyloxytropane methiodide (99a) and (-)-6β-acetyloxytropane methiodide (99b), (Scheme 25).

2.2.2. Some methods for the resolution of racemic modifications

The term "resolution" or "optical resolution" is generally defined as a procedure through which both optical isomers (enantiomers) are separated in the purified state from a racemic mixture. The striking discovery of hemihedrism in sodium ammonium tartrate had led Pasteur[26] to separate the enantiomers mechanically and to propose some hypothesis which established the foundation of stereochemistry. Pasteur suggested that a relationship might exist between the hemihedry of the tartrates and the optical activity of the substance in solution. He also pointed out that tartaric acid must possess asymmetry within the molecule itself, and that all substances fell into two groups, those which are superimposable on their mirror images and those which are not[26, 27]. Inspired by these important hypotheses of Pasteur, van't Hoff[28] and Le Bel[29] independently proposed the concept of the tetrahedral carbon atom



± (49) ± (51)

Resolution

(+)-6β-tropanol (-)-6β-tropanol

(+)-6β-acetyloxytropane (-)-6β-acetyloxytropane

(+)-6β-acetyloxytropane methiodide (99a)

(-)-6β-acetyloxytropane methiodide (99b)

Scheme 25

to explain the phenomenon of optical isomerism.

The prototypic Pasteurian separation of enantiomers from racemic modifications by mechanical means is very laborious and often crystals of enantiomers do not show morphological hemihedrism. Through years of investigation, Pasteur and his colleagues[30] developed various methods which are the main means of resolution today. These methods include (a) resolution by entrainment, (b) resolution *via* diastereoisomeric salt formation and (c) biochemical separation.

Resolution by entrainment[31] is also called preferential crystallisation and is used for preparative production of optically active substances industrially. This method involves the crystallisation of a supersaturated solution of the racemate inoculated with crystals of one enantiomer and is time and temperature dependent. It was recorded that from 1963 to 1973, 13,000 tons of L-glutamic acid was obtained by this method.

Resolution *via* diastereoisomeric salt formation[30] involves the interaction of racemic bases (B) with optically active acids (A) or racemic acids with optically active bases. Thus, enantiomers are transformed to diastereoisomeric salts which may then be separated by differential solubility in a certain solvent system (Scheme 26).

$$(+)\,A + (\pm)\,B \longrightarrow (+)A.(A)B + (+)A.(-)B$$

$$(+)B + (\pm)A \longrightarrow (+)B.(+)A + (+)B.(-)A$$

Scheme 26

The diastereoisomeric salts cropped after fractional crystallisation can then be hydrolysed with inorganic alkalis or acids to give the enantiomers. In general, tedious recrystallisations monitored polarimetrically are required. Common optically active acids used for resolution of racemic bases are tartaric acid, O,O-dibenzoyl-tartaric acid, mandelic acid, camphoric acid, camphor-10-sulphonic acid and α-bromocamphor-π-sulphonic acid. The optically active bases such as morphine, amphetamine, ephedrine and menthylamine are generally used for resolving racemic acids.

It is impossible to generalise on conditions which encourage resolution. Important considerations are the choice of solvent, and the type of optically active resolving agents used for the resolution of a particular class. However, often a resolving agent useful in separating isomers of one compound is ineffective for closely related structures. For example, the use of conditions which had succeeded in resolving (±)-trans-3α,6β-dihydroxytropane (21)[23] proved incapable of resolving (±)-6β-tropanol (51) in this work. Therefore, the resolution of each racemic mixture often constitutes an independent experimental system. A common problem encountered in the resolution process is the difficulty in inducing the diastereoisomeric salts to crystallize. Occasionally supercool conditions are employed to induce crystallization of unstable or oily diastereoisomeric salts[33]. Successful fractional crystallization under these circumstances may require temperatures as low as -20°C[34]. Even in crystalline form, some compounds, such as colchinol methyl ether, completely resisted resolution despite extensive work employing a variety of resolving agents and solvents[32].

As recognised by many investigators, resolution is still an empirical art and depends much on trial and error.

Another interesting method of resolution is the biochemical approach first discovered by Pasteur[30, 35]. Pasteur observed that when racemic ammonium tartrate was fermented with the mould Penicillium glaucum, the dextrorotatory salt was used up preferentially by the microorganism, leaving the corresponding levo-salt behind in the fermentation broth. The active principle in this biochemical asymmetric destruction are the enzymes of the microorganism. Biochemical kinetic resolution[36, 37] using enzymes for asymmetric destruction has found wide application in the preparation of some optically active amino acids. Hog kidney acylase is able to hydrolyse the L-isomer of racemic acyl-amino acids while leaving the D-isomer intact. Thus, the unchanged D-acyl amino acid can be extracted with ethyl acetate whereas the L-amino acid may be recovered by ion-exchange chromatography.

Besides these Pasteurian principles, asymmetric synthesis[38-40], in which the asymmetric atom is introduced during the reaction course, is sometimes employed to generate certain enantiomers. The principle underlying asymmetric synthesis is the stereoselectivity of the nucleophile (hydrides or organometallic reagents) during the addition to the planar carbonyl group. Cram's rule[38] suggests that the reagent (nucleophile) preferentially approaches the carbonyl group from a less hindered position, leading to the predominance of one stereoisomer (Fig. 13; the asymmetric carbon is in such an orientation that the carbonyl group is flanked by

two smaller groups (M and S). Then the reagent R'X attacks the carbonyl function from the side of the smallest group S).

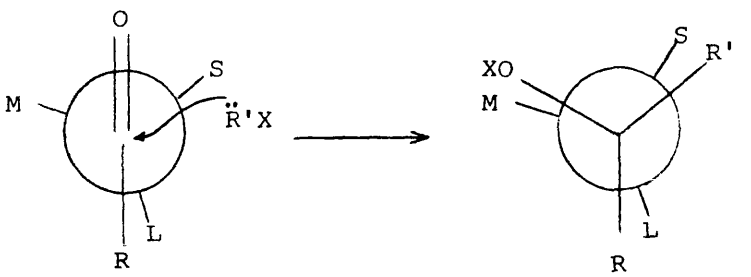


Fig. 13.

2.2.3 Resolution of (±) 6β-tropanol and the preparation of two optically active rigid acetylcholine mimics based on enantiotopic 6β-tropanols.

During the intensive investigations of the chemistry of tropanes in the '50's, the precursor of the 6-substituted tropanes, (±)-6β-hydroxytropinone (49), was resolved by Stoll, Becker and Jucker[22]. Fodor and Kovács[23] also reported the resolution of the precursor of valeroidine, (±)-trans-3α,6β-dihydroxytropane (21). However, the resolution of (±)-6β-tropanol has not been reported since the first synthesis of this racemic secondary alcohol by Jones and Pinder[24] in 1959. Thus, the attempt to resolve (±)-6β-tropanol in this work is not only aimed at the synthesis of optically active potential acetylcholine mimics, but also the continuation of a piece of work left by Fodor and others (see General Introduction) after their intensive explorations in tropane chemistry.

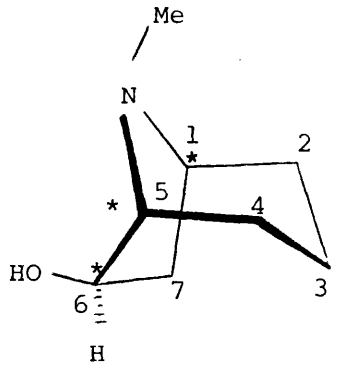


Fig. 14

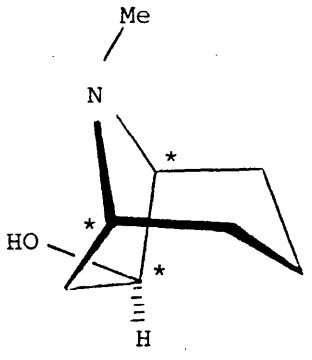


Fig. 15

Although 6β-tropanol (51) has three common centres of asymmetry, only one pair of enantiomers is possible (Fig. 14, S form; Fig. 15, R form). This is because the asymmetric centres at C-1 and C-5 are geometrically constrained at the bridgehead positions by the ring nitrogen in a symmetric pattern. Thus, one can imagine that in the absence of the 6-hydroxy group, the tropane molecule itself possesses a plane of symmetry (meso-form) and would be optically inactive.

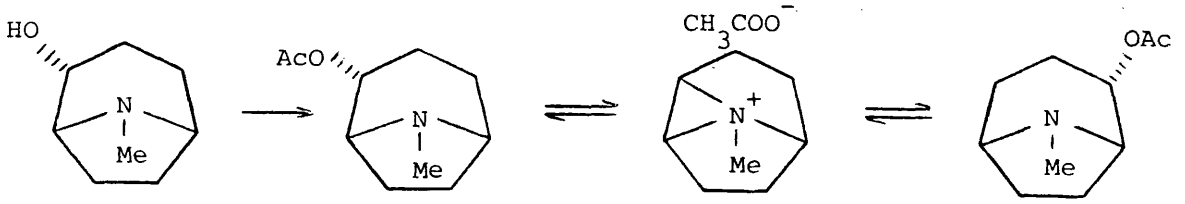
Initial attempts to resolve (±)-6β-tropanol were not successful. The diastereoisomeric salts formed by reacting the racemic base with d-mandelic acid resisted crystallization from a variety of solvents. With O,O-dibenzoyltartaric acid, the resulting diastereoisomeric salts crystallized from acetone/methanol mixture. However, these crystalline salts resisted further recrystallization.

After numerous attempts, the author found that (+)-6β-tropanol-(+)-10-camphorsulphonate preferentially crystallized from acetone/

isopropanol mixtures, whereas (-)-6β-tropanol(+)-tartrate preferentially crystallized from methanol/ethanol mixtures. The hydrochloride of (+)-6β-tropanol has a specific rotation of $+2.4^{o}$ and the hydrochloride of its enantiomer has a specific rotation of -2.3^{o}. The optical purity of the two enantiomers of 6β-tropanol was established by ^{1}H and ^{13}C NMR studies using a chiral shift reagent *in situ*. The result of this investigation will be described and discussed in Part 4 (also see Experimental,p.169).

Esterification of the (+)- and (-)-6β-tropanols with acetic anhydride/triethylamine at room temperature afforded, respectively, (+)-6β-acetyloxytropane and (-)-6β-acetyloxytropane. Mild conditions are necessary to avoid possible racemization at this step. Archer *et al.*[41] reported that when L(+)-2α-tropanol (12a) was esterified with acetic anhydride at refluxing temperature, racemization took place after a short period of time. To explain this, Archer *et al.* proposed the existence of an aziridinium intermediate (101) in the transition state of the racemization of L(+)-2α-tropanol (Scheme 27). The existence of such a hypothetical intermediate (101) has some support from the conversion of 5-aminocycloheptene (10) to racemic 2α-tropanols *via* a bridged aziridine (11)[42], (see General Introduction, Section A(b)).

Quaternization of the enantiomers of 6β-acetyloxytropane gave the corresponding methiodides. These optically active methiodides have much higher melting points ($256^{o}C$) than the racemate (±)-6β-acetyloxytropane methiodide ($206^{o}C$).



(12a) (+) (101) (-)

Scheme 27

Theoretically, chromic acid oxidation of the (+)- and (-)-forms of 6β-tropanol followed by hydrogenation[25] could give the (+)- and (-)-enantiomers of 6α-tropanol. However, owing to the fact that only small quantities of pure enantiomers of 6β-tropanol was isolated, this work has not been carried out. Besides, the chromic acid method should be replaced by other mild oxidation methods to avoid racemization in this step.

2.2.4 Pharmacological results and discussion

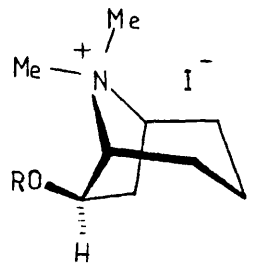
Cholinergic agonistic activities were tested on isolated rabbit duodenum and guinea pig ileum. It was found that (+)-6β-acetyloxytropane methiodide, (-)-6β-acetyloxytropane methiodide, and the corresponding racemic compound (99) were virtually inactive on these preparations. The methiodides of (±)-6β- and (±)-6α-

tropanols were also found to be inactive. The racemic (±)-6α-acetyloxytropane methiodide (100)[25], on the other hand, was found to be a very weak cholinergic agonist on guinea pig ileum preparation. The ED_{50} of (100) is 631 ng ml^{-1} whereas that of acetylcholine is 50 pg ml^{-1}. In addition, the action of (100) was unaffected by the administration of hexamethonium which is a highly specific ganglionic blocking agents, showing that (100) is a muscarinic agonist.

The inertness of the enantiomers of (99) and the weak activity of (100) also add to our understanding that among rigid muscarinic agonists, as exemplified by the ACTM series[18, 19], the 3-trimethylammonium-2-acetyloxybicyclo[2,2,2]octane iodide series[20, 21], the 2-acetyloxytropane methiodide series[17], and the 6-acetyloxytropane methiodide series of the present work (Table 4), the transoid forms are exclusively muscarinic agonists, whereas those corresponding to the cisoid forms are, in general, inactive.

These findings support the view that the torsion angle τ2 be within the antiplanar to anticlinal range (± 180° and ± 120° respectively) for muscarinic activity[14, 15]. Close consideration of the structural features of the most potent member of rigid acetylcholine mimics, S(+)-trans-ACTM, suggests that this molecule has much smaller steric requirements than members of other series. The fact that S(+)-trans-ACTM(90)[18,19] is much more potent than its enantiomer, R(-)-trans-ACTM (94), indicates that the orientation of hydrophobic groups in the molecule itself as well as its steric requirements would have a marked effect on agonistic

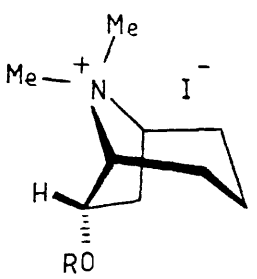
Table 4. Cholinergic agonist activities of some 6-substituted tropane methiodides.



(1) Agonistic activities on guinea pig ileum ($\mu g\ ml^{-1}$)

(2) Agonistic activities on rabbit duodenum ($\mu g\ ml^{-1}$)

Compound No.	R	Chirality	(1) $I.D._{50}$	(2) I.D.
99	CH_3CO-	(±)	>10	-
99a	CH_3CO-	(+)	>10	
99b	CH_3CO-	(-)	>10	
102	-H	(±)	-	-



Acetylcholine:

(1) $I.D._{50} = 5 \times 10^{-5}\ \mu g\ ml^{-1}$

(2) I.D. = 0.005 - 0.1 $\mu g\ ml^{-1}$

Compound No.	R	Chirality	(1) $I.D._{50}$	(2) I.D.
100*	CH_3CO-	(±)	0.63	1-40
103	-H	(±)	-	

*Compound (100), 1 $\mu g\ ml^{-1}$; unaffected by hexamethonium bromide, 10 $\mu g\ ml^{-1}$ in (1); the same compound (100), 40 $\mu g\ ml^{-1}$, unaffected by hexamethonium bromide, 1 $\mu g\ ml^{-1}$ in (2). In both test systems, the action of nicotine (87) was completely blocked in the presence of hexamethonium.

activity. It follows that the high stereoselectivity of the muscarinic receptor must be conferred by the orientation of certain hydrophobic groups in the receptor site providing steric hindrances to ligands which do not fulfil its stereochemical requirements.

The weak activities of the 6-acetyloxytropane series is hence attributed to the enormous steric requirements of the propyl bridge of the 6-membered piperidine ring. This view is supported by the argument that despite the similar stereochemical parameters of (±)-6α-acetyloxytropane methiodide (100) and (±)-2α-acetyloxytropane methiodide (97)[17] viz. τ2 of both species lies within the anticlinal range and the interatomic distance between cationic centre and esteratic oxygen of both equal to 3.6 Å approximately, (97) is about 100 times more active. This may be due to the fact that the steric effect of the ethylene bridge in the 5-membered ring of the 2-substituted tropanes is less than that of the propyl bridge in the 6-membered ring of 6-substituted tropanes. Besides the weak activities are also attributed to the fact that these rigid 6-tropane salts are deficient of the $Me_3\overset{+}{N}$- structural unit common to virtually all potent muscarinic agonists.

According to the structure-activity relationships of the rigid mimics of acetylcholine, it is feasible to propose a model for the muscarinic receptor site.

In the proposed muscarinic receptor model (Fig. 16), the esteratic centre is suggested to be embedded below the hydrophobic surface of the receptor. Hydrophobic zones A and B denote the

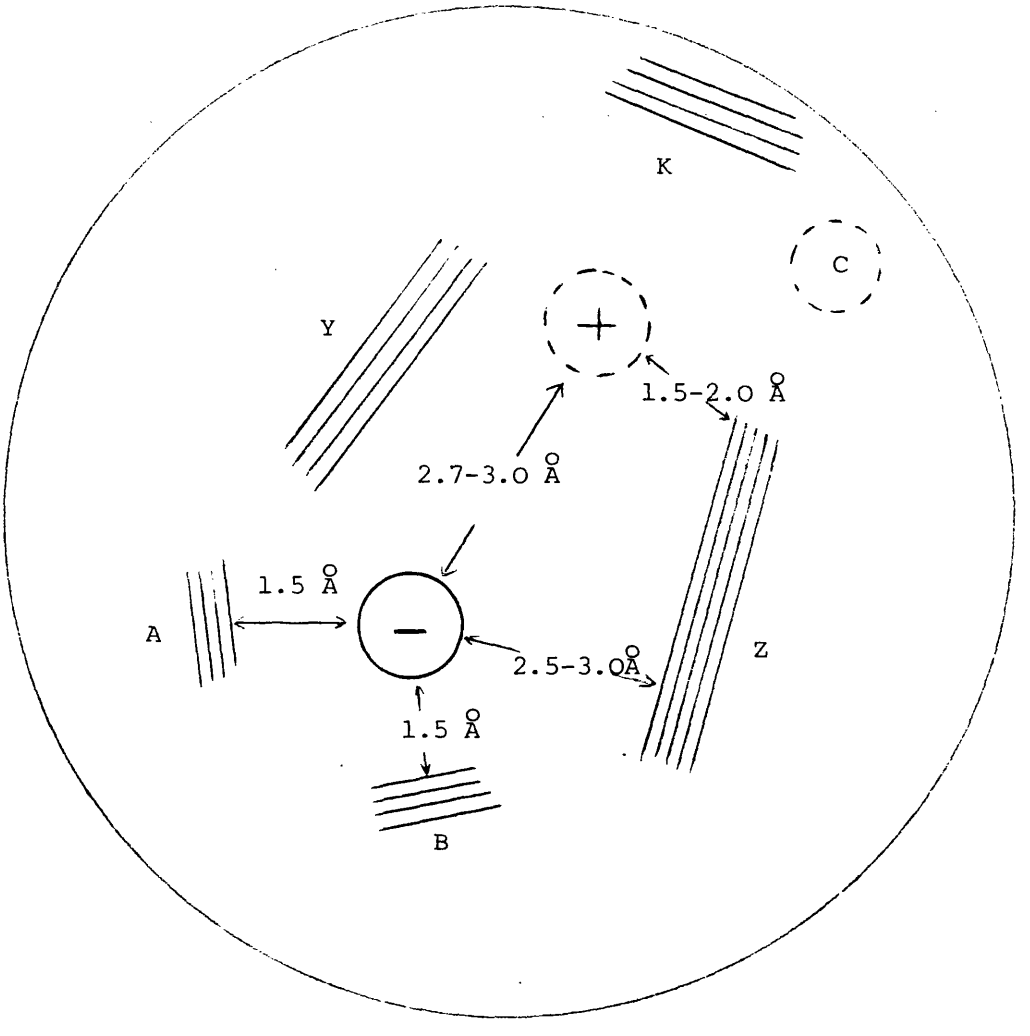


Fig. 16. ⊖ and ⊕ denote the anionic centre and the esteratic centre respectively, ≡ denotes hydrophobic sites)

sites for interacting with the $\underline{N}^{+}$-Me groups. Zone Z denotes the site for interacting with the hydrophobic groups (H side) of the molecule [Fig. 17, the carbon atoms belonging to (90) are labelled ACTM; to (89) as β; to (86) as M]. The interatomic distance between the anionic centre and esteratic centre is suggested to be smaller than 3.0 Å to allow a "induced fit"[43]

of the acetylcholine molecule so that C-4 and C-5 would be forced to the H side of the molecule and thereby triggers the response on interaction with Zone Z of the receptor site. Conformational change is then envisaged which initiates those biochemical events leading to tissue response. Another cationic site (denoted by (C)) orientated below the receptor surface may be available for interacting with the carbonyl oxygen of the acetyl group. Additional hydrophobic sites Y and K may be orientated in the locations shown in Fig. [16] which hinder bulky molecules from approaching the active sites.

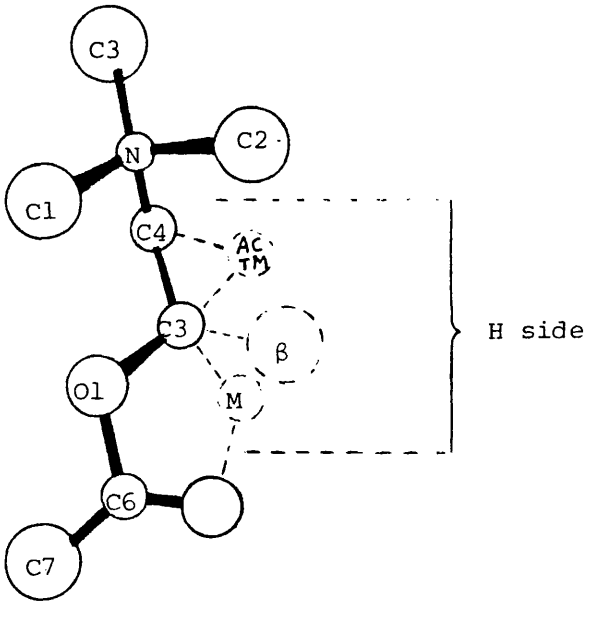


Fig. 17

Apart from stereochemical investigations of the acetylcholine receptor, biological and biochemical findings also add to our knowledge of the diverse features of the receptor. Acetylcholine receptors were isolated from the electric ray Torpedo electroplax and the electric eel Electrophorus electricus[45-51]. Purification

of the receptors was carried out by conventional column chromatography, affinity chromatography[52] and ion-exchange chromatography[53]. The molecular weight of the purified receptor from Electrophorus was established by gel electrophoresis, to be 275,000. SDS-gel electrophoresis of the receptor under denaturing conditions suggested that the receptor is composed of five subunits[54]. This suggestion is consistent with direct observation of the receptor by electron microscopy which indicates the presence of 5 - 6 subunits in the rosettes[55, 56].

It was reported that the cholinergic receptor of the electric eel contains 46% polar amino acids[57, 58] and the suggestion was made that the hydrophobic nature of the receptor is due to an asymmetric distribution of the polar amino acid residues. Phosphatidylinositol (PI) is the most conspicuous phospholipid bound to the protein receptor[59] and acetylcholine causes an increased incorporation of ^{32}P and of labelled inositol into the PI of the nerve-ending fraction from brain[60]. Lunt et al.[61] suggested that after acetylcholine has interacted with the receptor site and induced conformational change, the PI pool is then associated with the receptor. Carbohydrates and their complexes were also found in the receptor[62]. Atomic absorption studies[63] suggest that the receptor contain 4.7% by weight of bound calcium ions.

Binding studies[64, 65] of the muscarinic receptor using reversible ^{3}H-antagonists such as propyl-benzilylcholine indicate that the Hill coefficients do not differ from the theoretical

value of 1.0 (The Hill plot is % occupancy versus log ligand concentration). It was concluded that the antagonists bind to a single class of receptor sites[64]. On the other hand, the binding curves of agonists[64, 65] deviate substantially from the simple mass action-determined process as characterized by low Hill coefficients (0.33 and 0.42 for carbachol and acetylcholine respectively). Thus, it was suggested[67] that at least three classes of agonist binding sites exist, and that negatively cooperative interactions of the receptor subunits are involved.

Based on the sequential model of Koshland[44] and the hypothesis of Birdsall, Burgen and others[65, 66], a kinetic model can be proposed for the muscarinic receptor (Fig. 18). Two conformational states, one with high affinity binding constant (K_H) and one with low affinity binding constant (K_L) are available for the receptor subunits. Binding of the first agonist molecule induces conformational changes in the first subunit as well as in the second subunit, lowering the binding affinity of both subunits. These sequential events pass from the second subunit to the third, and so forth (Fig. 18).

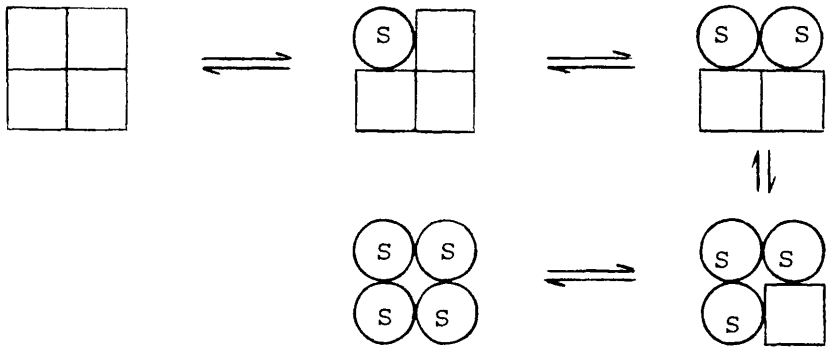


Fig. 18. (S denotes substrate molecule, □ denotes receptor conformational state with high affinity binding constant K_H and ○ denotes conformational state with low affinity constant K_L).

This sequential model, which is based on negative cooperativity agrees well with the slow rate of acetylcholine action mimiced by muscarine in the heart, smooth muscle and exocrine gland where a mild and slow response is indispensable.

However, the hypothesis of negative cooperativity in muscarinic receptor subunits is complicated by some paradoxical findings from further binding studies, and investigations are still carrying on[67].

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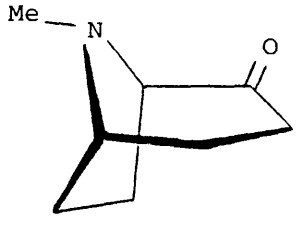
Part 3.. Stereochemical studies on the reductions of 6-phenyl-6-tropene and Hofmann elimination of 6α-phenyltropene methiodide.

3.1 Introduction

The stereochemical course of reductions of tropan-2-one (104) and tropan-3-one (3) were well studied[1-5]. Bell and Archer[1] reported that in the reduction of tropan-2-one, the use of sodium and alcohol produces 2β-tropanol (105) whereas with lithium aluminium hydride, 2α-tropanol (12) is the major product. Beckett et al.[2] described the reduction of tropan-3-one under varying conditions of time, temperature, solvent and reducing agent. It was concluded[2] that the stereoisomeric composition of reduction products [tropine (14) and ψ-tropine (15)] is independent of the reagent and temperature and that kinetic and thermodynamic factors are involved.



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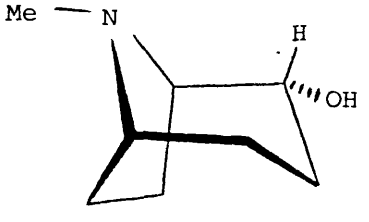
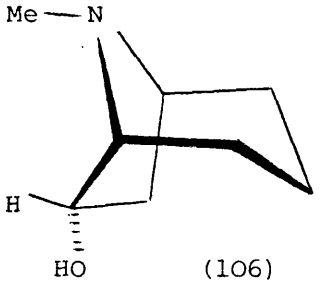


(105)



(106)

Aaron and Reiff[4] reported that the catalytic hydrogenation of tropan-6-one (52) gives exclusively 6α-tropanol (106) in a 99% yield, indicating that highly stereospecific processes are involved (see Section 3.2.2)

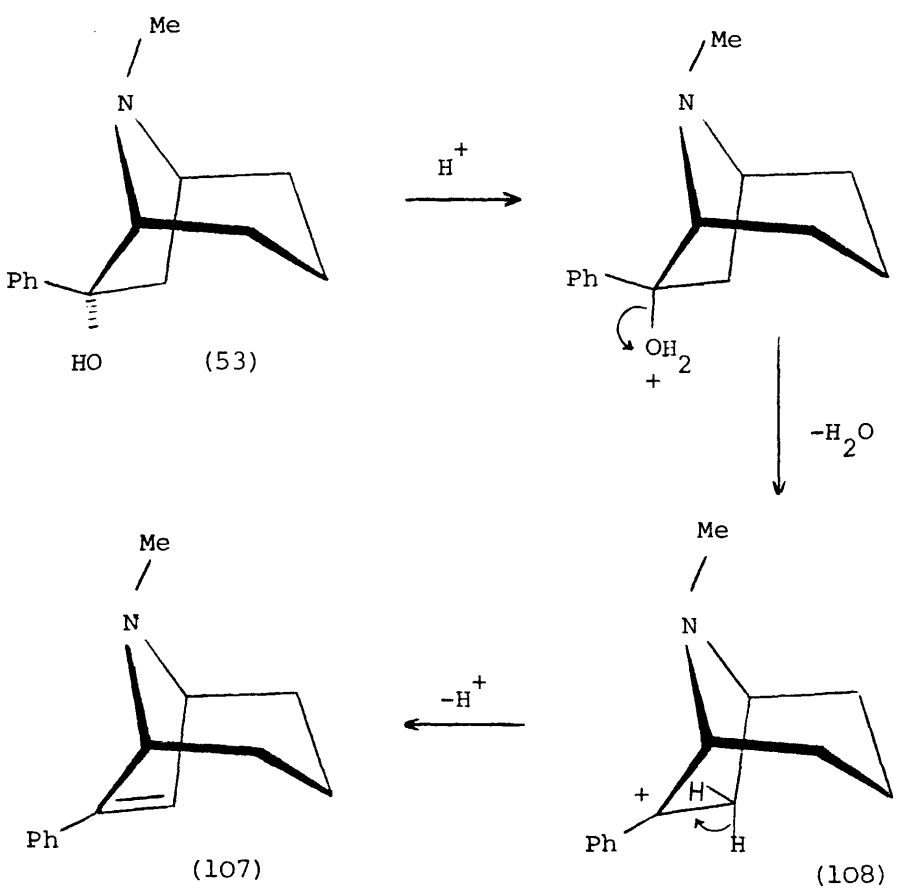
On the other hand, stereospecific reduction studies on olefins of 6-aryltropanes have not been reported. In this work, the olefin 6-phenyl-6-tropene (107) was obtained by dehydration of 6β-phenyl-6α-tropanol (53; R = H). Catalytic hydrogenation of (107) and lithium aluminium hydride reduction of this olefin (107) gave products of stereochemical interest. Attempts to elucidate the unknown structure of a major product from lithium aluminium hydride reduction of 6-phenyl-

6-tropene have in turn prompted the study of a stereospecific cis-Hofmann elimination reaction. These investigations will be described and discussed in the following sections.

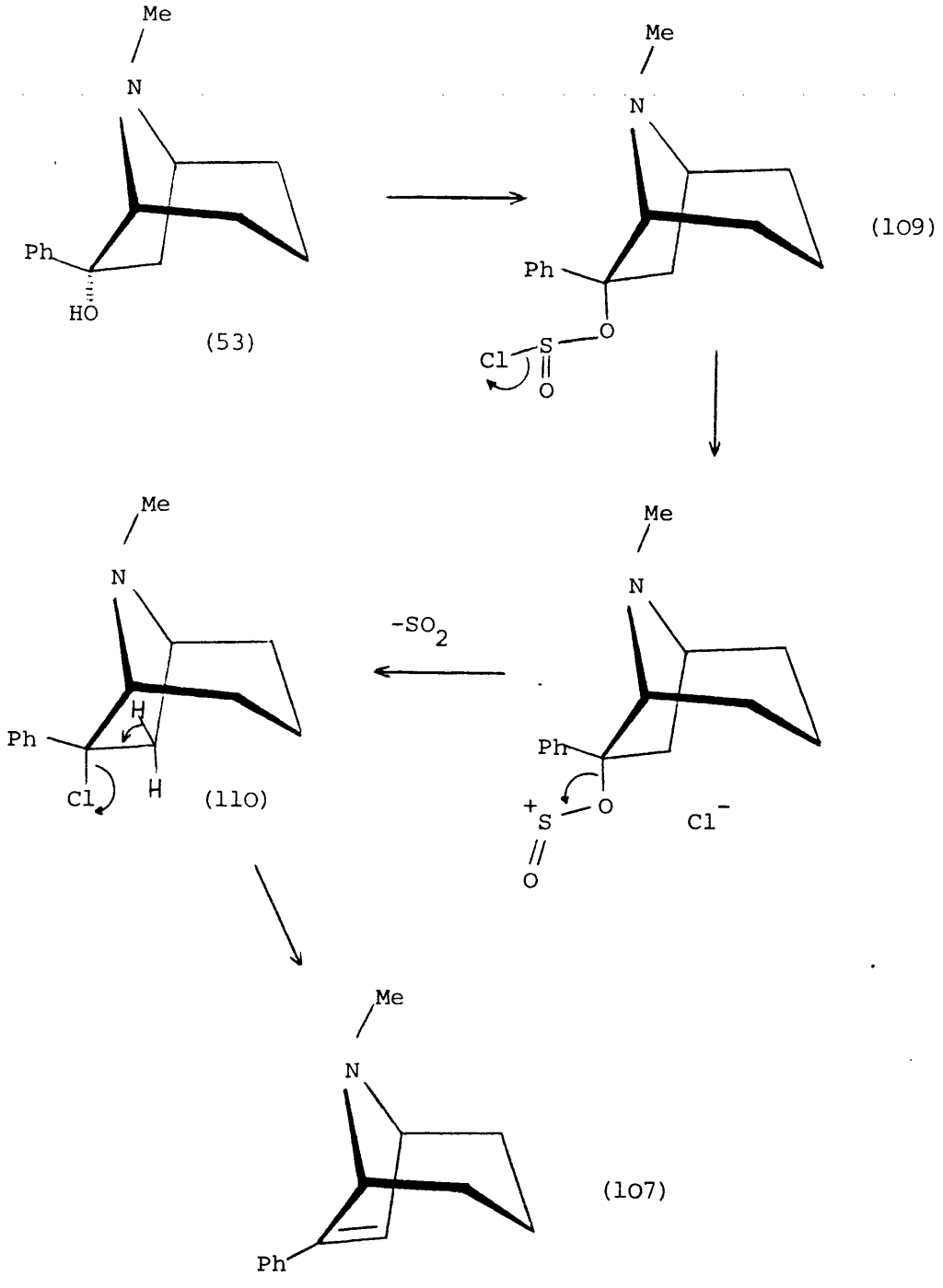
3.2 Discussion

3.2.1 Synthesis, reactions and stereochemistry of 6-phenyl-6-tropene

The first reported synthesis of 6-phenyl-6-tropene (107) was accomplished by acid-catalysed dehydration of (53; R = H) using concentrated sulphuric acid[6]. This process is considered to proceed via a two-step El mechanism in which the carbonium ion (108) generated is stabilized by the strong +I inductive effect of the phenyl group (Scheme 28).



Scheme 28

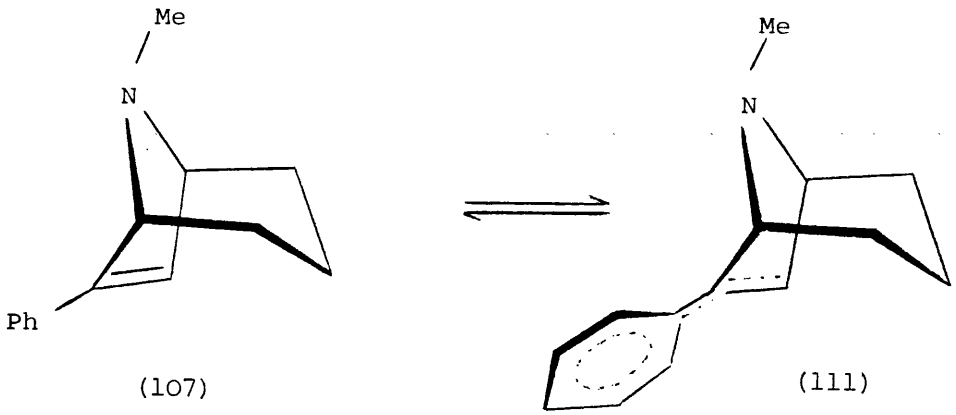

Me
N
Ph
HO
(53)
Me
N
Ph
O
Cl
S
O
(109)
Me
N
Ph
O
+S
O
Cl⁻
-SO2
Me
N
Ph
H
Cl
H
(110)
Me
N
Ph
(107)

Scheme 29

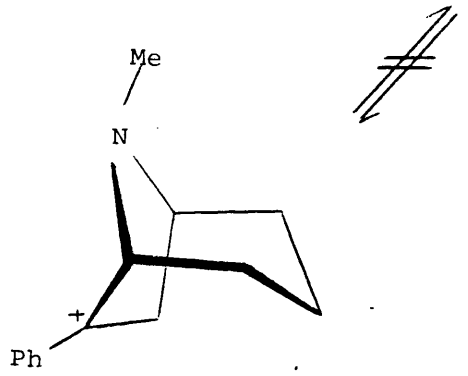
The synthesis of the olefin (107) in this work employed Darzens' procedure[7]. This method involves the reaction of the tertiary alcohol (53) with thionyl chloride to form the chlorosulphite (109) which then proceeds *via* a S_N2 mechanism to form the tropane chloride (110). Subsequent dehydrohalogenation in alcholic KOH *via* a fast E2 process afforded the olefin (107) in a 75% yield (Scheme 29).

Attempts were made to synthesize the 6α-phenyl-6β-tropanol by hydrating the tropene (107). However, this olefin (107) was found to be resistant to the process of hydration, including sulphuric acid hydration[8], formic acid hydration[8], and oxymercuration-demercuration procedures[9-11]. This is attributed to the fact that the double bond of (107) is conjugated to the aromatic ring system, which makes difficult the formation of the carbonium ion intermediate (108) necessary for the hydration process (Scheme 30). Similar resistance to hydration was reported by Brown and Geoghegan[11] on cyclic olefins such as 1-phenylcyclohexene (112) and 1-phenylcyclopentene (113).

There is evidence for the existence of the resonance form (111) from ^{13}C NMR studies of this phenyltropene (see Part 4). It is suggested that the p-orbitals at C-7, C-6 and that of the aromatic ring overlap successively with one another so that the π cloud is delocalized between these carbon atoms. For maximum overlap of these p-orbitals, the phenyl ring is suggested to be in a coplanar orientation[12] with the 6-olefinic bond of (107).

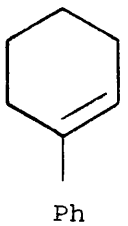


(107) (111)

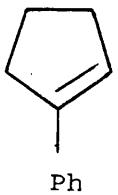


(108)

Scheme 30



(112)



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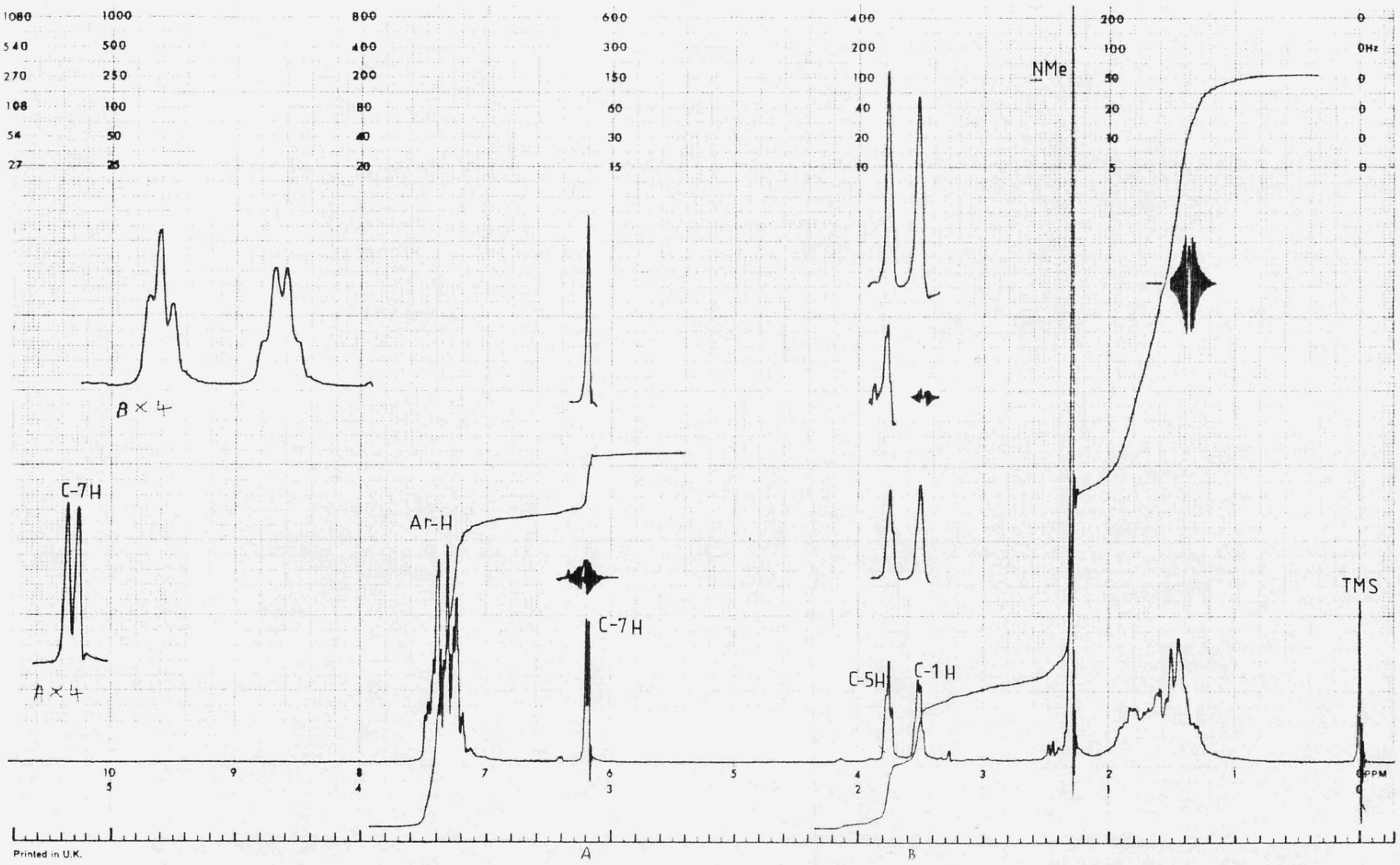
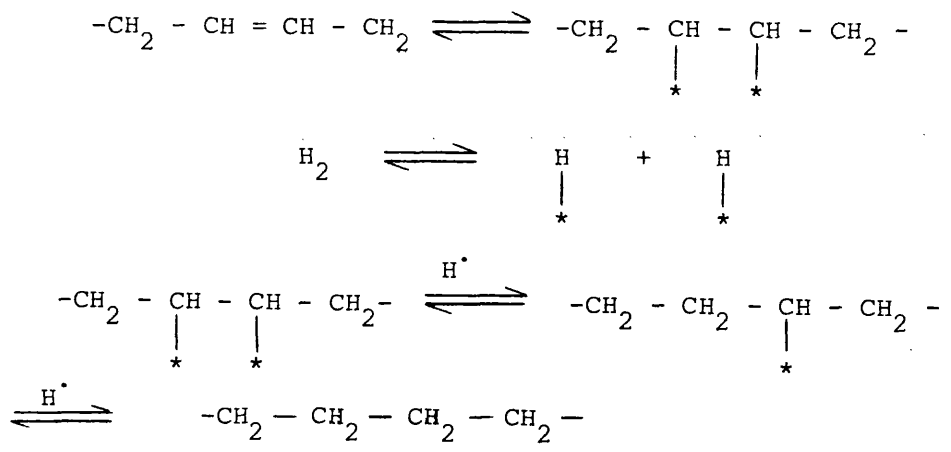


Fig. 19. ^{1}H NMR spectrum of 6-phenyl-6-tropene (107) in $CDCl_3$.

Application of Bredt's rule[13] suggests that the double bond is located between C-6 and C-7 of this phenyltropene. This is further supported by the occurrence of two distinct bridgehead proton signals centred at δ3.50 and δ3.75 of the ^{1}H NMR spectrum of (107), (Fig. 19).

3.2.2 The stereochemical course of catalytic hydrogenation of 6-phenyl-6-tropene

The mechanism of catalytic hydrogenation is complex and is still controversial. The early "nascent hydrogen" hypothesis was negated by evidence showing that molecular hydrogen alone is not involved in reduction at high hydrogen overvoltage surfaces[14]. A generally accepted current theory suggests the adsorption of the substrate such as an olefin to the metallic catalyst surface forming a chemisorption complex[15-17]. Willstätter[18] and Ingold[19] envisaged that electrons are being transferred from the surface of the chemisorption complex to the substrate. The classical hydrogenation model of Horiuti and Polanyi[20] suggests that the olefin is diadsorbed on two adjacent catalyst sites (denoted by *) and hydrogen is also dissociatively adsorbed on two catalyst sites. Stepwise addition of hydrogen radicals to the adsorbed carbon radicals give the saturated hydrocarbon (Scheme 31).



Scheme 31

Another more current theory[21], which is an extension of the classical model of Horiuti and Polanyi, interprets the mechanism of hydrogenation as hydrogen transfer between an adsorbed hydrocarbon species and the adsorbed olefin. This self-hydrogenation process is suggested to be continuous in the presence of added hydrogen.

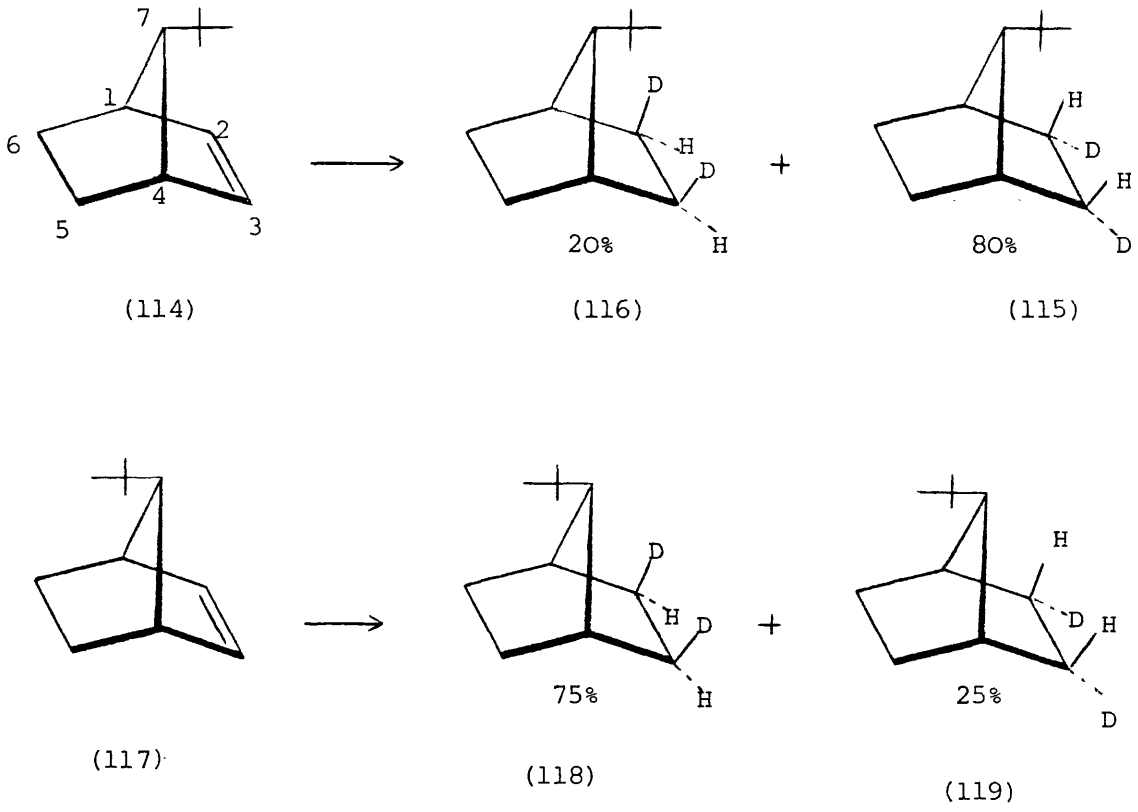
Certain studies suggest that the stereochemical course of catalytic hydrogenation is rather complex. There is evidence suggesting that the adsorbed hydrocarbon is π-bonded to the catalytic sites so that adsorbed sp^2 carbon atoms have a planar configuration[22]. Therefore, these planar centres can react with hydrogen radicals at their upper or lower face, leading to cis-addition, trans-addition or 'bottom-side' addition of hydrogen radicals. In general, cis-addition products predominate, with hydrogen approaching from the less hindered side of the unsaturated substrate[17]. These facts are hence consistent with the hypothesis that a chemisorption

complex is involved in the hydrogenation process. Trans-addition products may predominate in the reduction of sterically hindered olefins.

It appears that in many cases "catalyst hindrance"[17] is a major factor in determining the stereochemical nature of the products. The term "catalyst hindrance" was suggested by Adkins and his colleagues[22] who observed that various substituted diphenyl compounds with restricted rotation could not be hydrogenated under drastic conditions, whereas those diphenyl compounds with free rotation could be hydrogenated. Linstead et al.[17] attributed this fact to the inability of the restricted molecule to lie in one plane, leading to inhibition of the adsorption process by the catalyst.

Studies of the hydrogenation of a number of bridged polycyclic systems[21-25] suggest, in general, an exosteric course of reaction. Baird and Surridge[26] reported that exclusive exo-cis-addition of hydrogen occurs with 7-substituted norbornenes when the substituent is small. However, hydrogenation of syn-7-tert-butylnorbornene (114) with deuterium gas gives 80% endo products (115) and 20% exo products (116) whereas with anti-7-tert-butylnorbornene (117) there is 75% exo product (118) and 25% endo product (119),(Scheme 32.) These results are consistent with Linstead's catalyst hindrance hypothesis[17] since the enormous steric requirement of the syn-7-tert-butyl group of (114) would inhibit the approach of the catalyst via an exosteric course.

However, in the gas phase or in non-polar solvents, hydrogenation of certain aromatic and cyclo-olefinic hydrocarbons over palladium

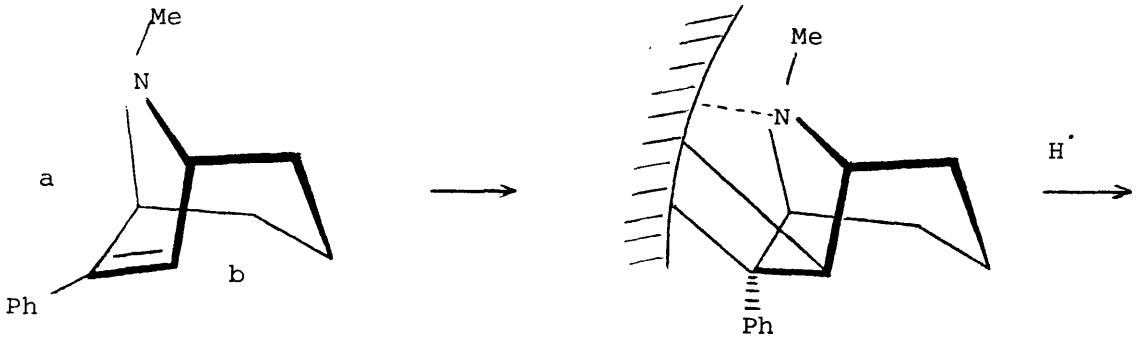


Scheme 32

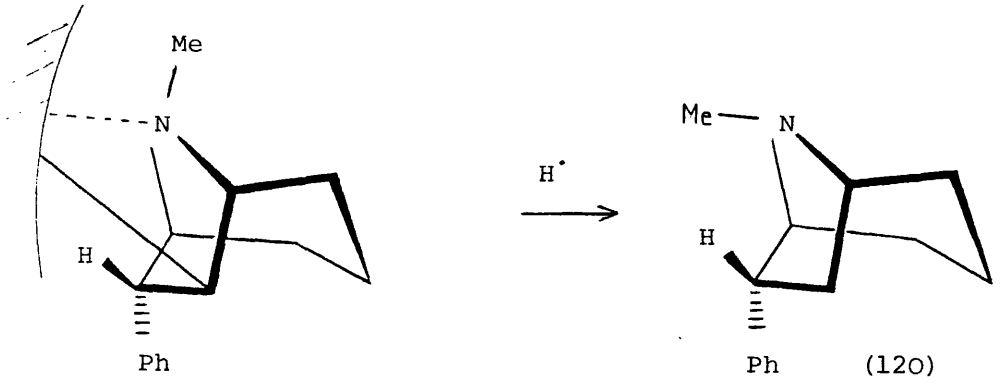
sometimes proceeds with addition of hydrogen from that side of the molecule opposite to the catalyst (bottom-side addition)[27]. It was suggested[27] that only the substrate is chemisorbed on the catalyst and the hydrogen comes from the reaction medium .

The hydrogenation of 6-phenyl-6-tropene (Scheme 33) in this work[28] was effected under a hydrogen pressure of 60 p.s.i., catalysed by palladium charcoal. The ^{1}H NMR spectrum of the reduced product indicated the disappearance of the olefinic doublet at δ6.19 which is characteristic of the olefin (107). The configuration of the 6-phenyl group of the reduced product (120) is established as α- by ^{1}H NMR studies of the tertiary base (120) and its methiodide (126), (see Part 4)).

Of interest, in the hydrogenation of the olefin (107) and the ketone tropan-6-one (52; P 33)is that the stereoisomeric composition of the reduced product in both cases is exclusively the α-isomer [6α-phenyltropane (120) and 6α-tropanol (106)] respectively. This indicates cis-addition of hydrogen radicals on the olefin (107) via an exosteric course (Scheme 33).



(107)



(120)

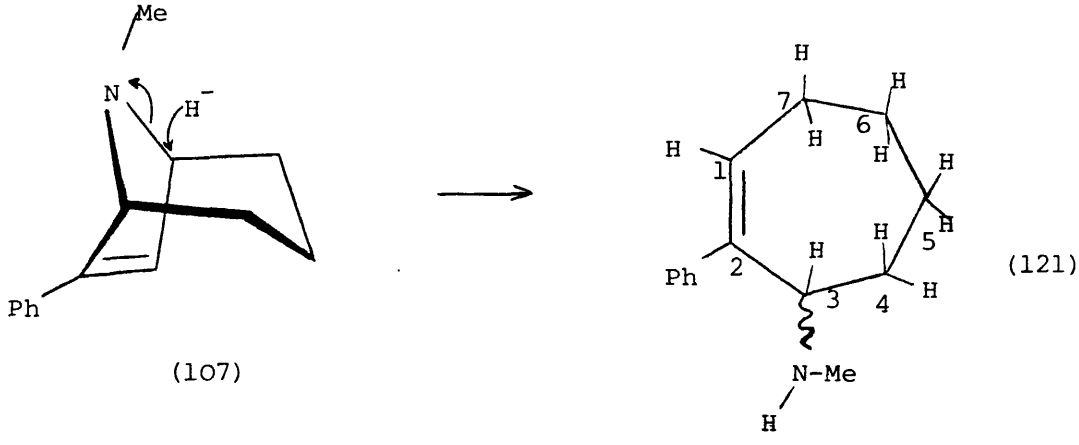
Scheme 33, a denotes exosteric side, b denotes endosteric side, shaded parts represent catalyst sites.

Two factors are considered to control this stereospecific hydrogenation process. It was suggested[3] that during the reduction of tropinones (tropan-2-one, and tropan-3-one), steric factors may operate either by hindering approach of the catalyst or by destabilizing the transition state of reduction. In the case of 6-substituted tropanes, it is suggested[28] that the endosteric side (side b) is

the more sterically hindered side by consideration of the hindrance contributed by C-3 and the axially orientated 3α-proton. In addition, the ring nitrogen may coordinate with the metal catalyst and thereby direct an exosteric cis-addition of hydrogen radicals on the activated C-6 and C-7 alkyl radicals of the tropane during the chemisorption transition state (see Scheme 33).

3.2.3. Structure elucidation of the major product and mechanistic studies of lithium aluminium hydride reduction of 6-phenyl-6-tropene.

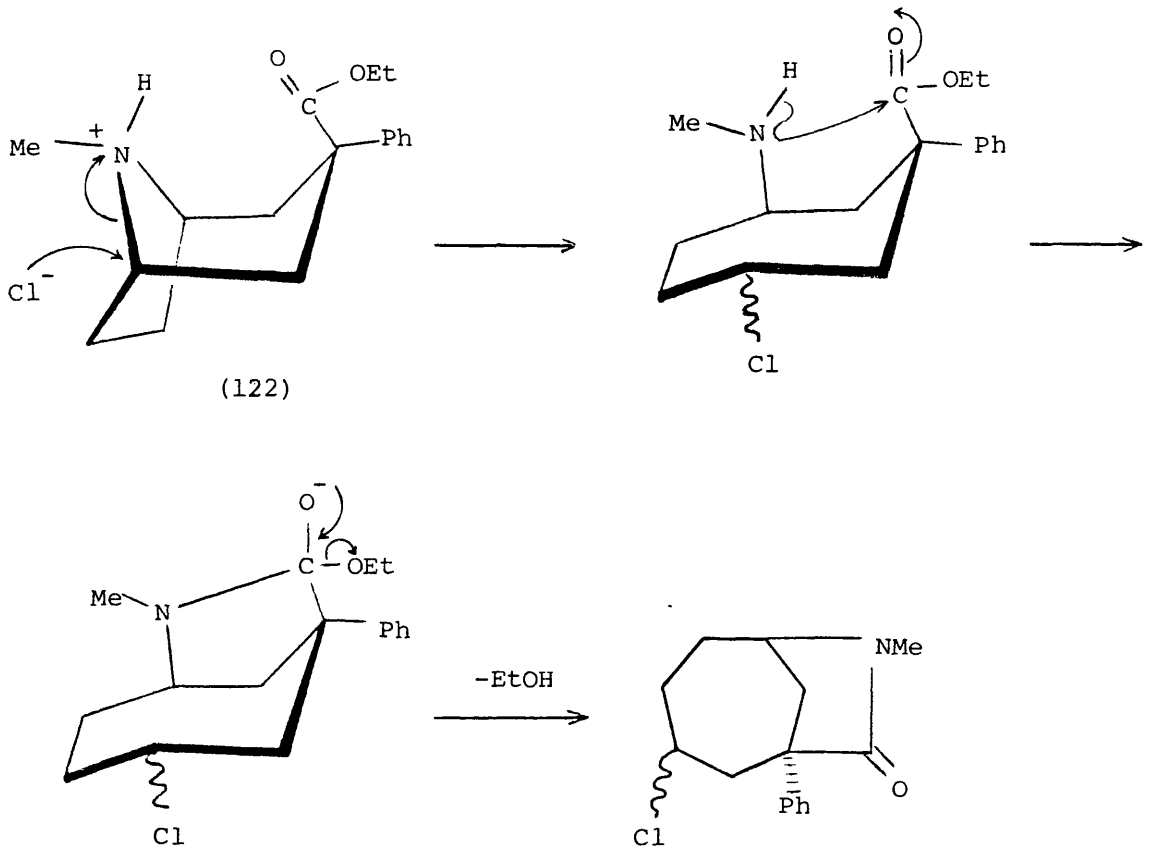
It is known that metallic hydrides such as lithium aluminium hydride do not usually attack the olefinic bond unless it is polarized by electron withdrawing substituents[30]. Since the tropane olefin (107) has its double bond conjugated with a phenyl ring, early investigations[6] were carried out on the reaction of lithium aluminium hydride with the olefin (107) in tetrahydrofuran as solvent. The structure of the product (121) and the mechanism proposed at the time for its synthesis are presented in Scheme 34.[6]



Scheme 34

This mechanism (Scheme 34) is analogous to the pyrolysis of a tropane analogue of pethidine (122), (Scheme 35).[31] In both cases

a nucleophile attacks the bridgehead position resulting in ring-opening (in the case of Scheme 35, there are further rearrangements following initial ring opening).



Scheme 35

However, information emerged from a decoupled ^{1}H NMR spectrum of the reduction product (Fig. 19) led the author to propose an alternate mechanism(Scheme 36), with a different product structure (123). The crucial point indicated by the ^{1}H NMR spectrum (Fig. 19) is that the olefinic triplet signal of the reduction product is coupled to a region of multiplets resonating at δ1.96 and not to the group of multiplets resonating at a lower field region of δ2.50 - δ2.70 These NMR evidences are thus not consistent with structure (121) since the C-7 protons to which the olefinic proton (C1-H) is coupled to should resonate at a lower field position than C4-H, C5-H and C6-H.

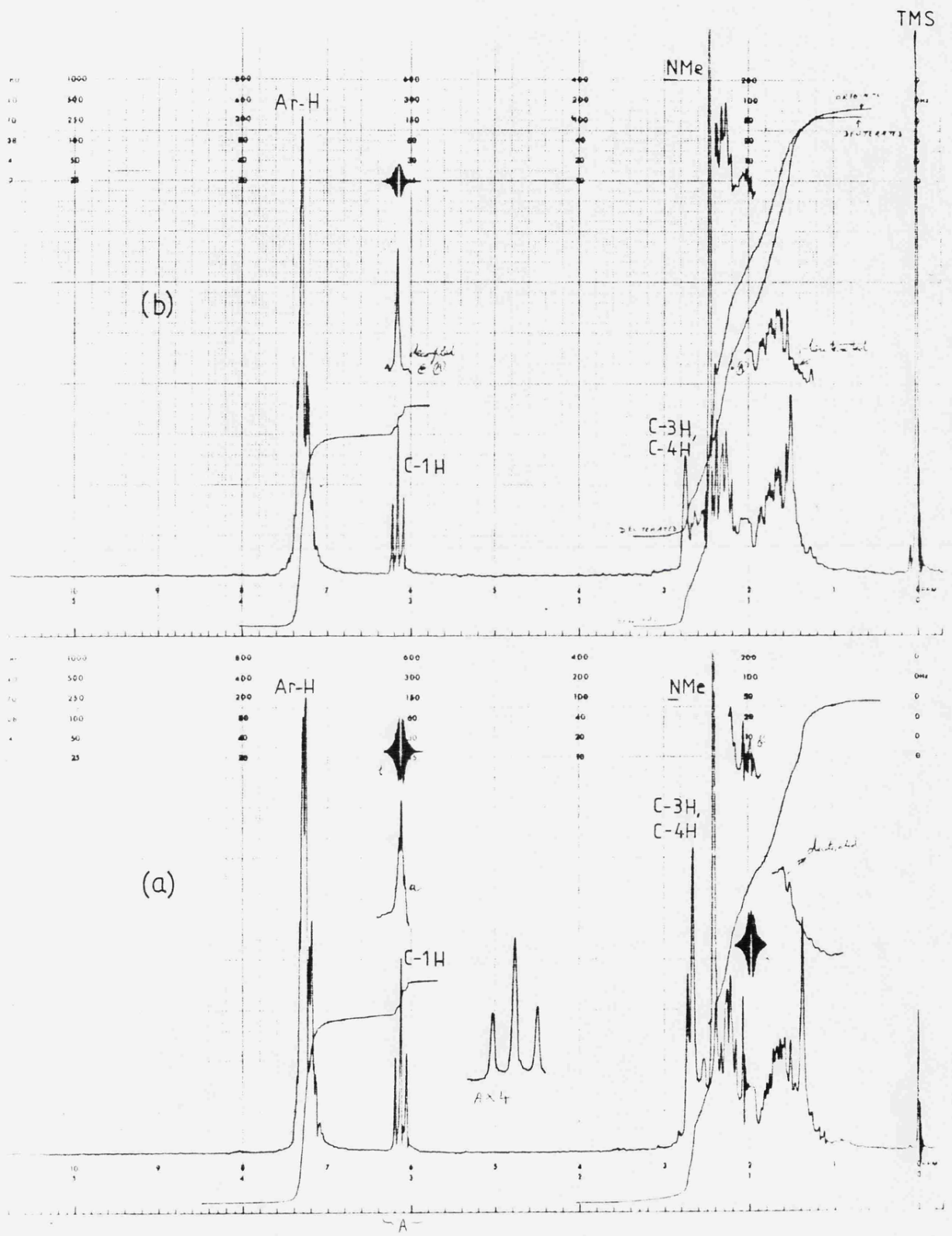
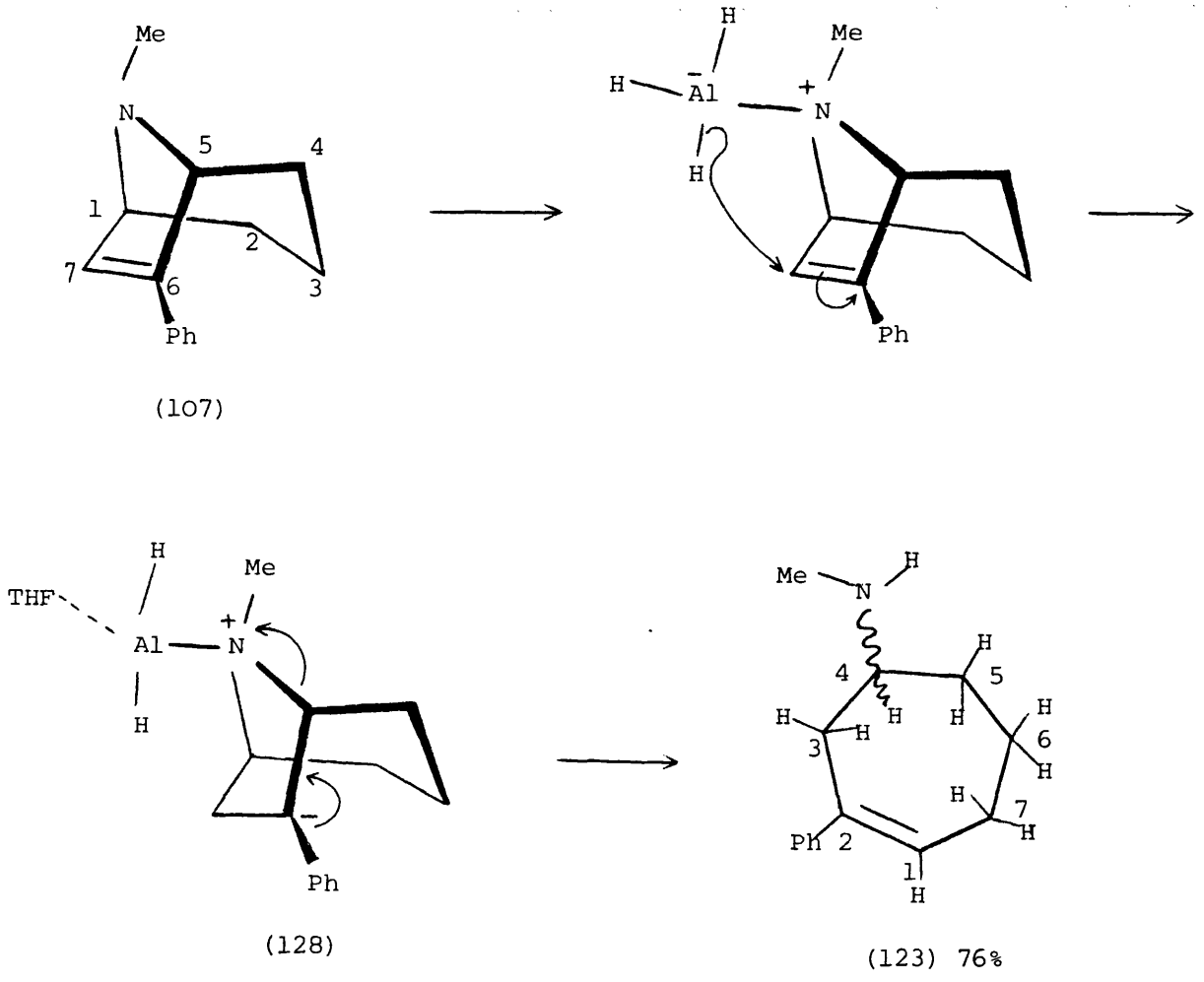


Fig. 20. (a) ^{1}H NMR spectrum of 4-methylamino-2-phenylcycloheptene (123) in $CDCl_3$

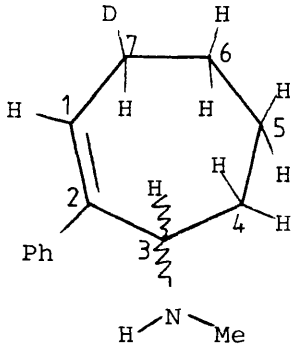
(b) ^{1}H NMR spectrum of 3-deutero-4-methylamino-2-phenylcycloheptene (125) in $CDCl_3$.



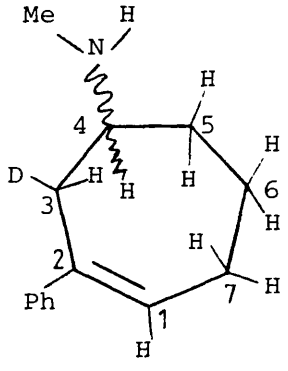
Scheme 36

In the alternate proposed structure (123), it is quite clear that the methylene signals (C-7H) to which the olefinic triplet is coupled would be resonated at a higher field region than the methylene signals (C-3H) by a consideration of the combined electron withdrawing effects of the olefinic bond, the phenyl group and the adjacent C-N group.

One attempt to establish the structure of the reduction product involved reacting the olefin (107) with lithium aluminium deuteride. It was predicted that if (121) represents the correct structure, then the olefinic signal of the deuterated product (124) will become a doublet in the ^{1}H NMR spectrum (see Scheme 34). However if (123) represents the correct structure, then the olefinic triplet signal will be retained in the ^{1}H NMR spectrum of the deuterated product (125).



(124)



(125)

In addition, it was considered that if (125) is the correct structure of the deuterated product, then the lower field multiplet signal at δ2.67 will diminish in intensity since one of the protons at C-3 will be replaced by a deuterium atom.

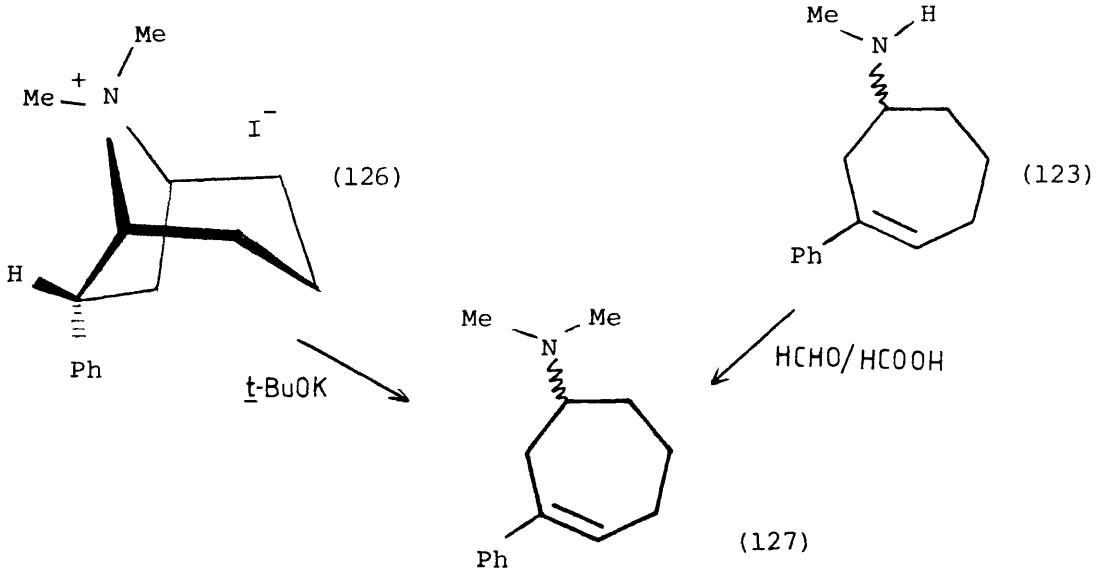
In the ^{1}H NMR spectrum (Fig.20b) of the deuterated product, there is retention of the characteristic olefinic triplet and also significant reduction in intensity of the multiplet resonating at δ2.67, which would be indicative of structure (125). Besides, these evidences also support structure (123) and the hypothetical mechanism (Scheme 36). The ^{13}C NMR spectrum of (123) shows a singlet at δ38.3

for C-3, whereas in (125), the C-3 signal appears as a triplet centred at δ38.2 corresponding to spin 1 of the deuterium nucleus[32] (see Fig. 21 and Fig. 22, also Part 4).

Mass spectra of (123) and (125) indicate molecular weights of 201.1503 and 202.1571 respectively, corresponding to molecular formulae of $C_{14}H_{19}N$ and $C_{14}H_{18}DN$ respectively (see Experimental).

Conclusive evidence of the structure (123) came from studies[28] of the reaction products of Hofmann elimination of 6α-phenyltropane methiodide (126) and N-methylation of (123). It was found that both reactions lead to the same product (127) as indicated by ^{1}H NMR and ^{13}C NMR studies of purified reaction product in each case. (see Scheme 37; Fig. 23 and Fig. 24).

Therefore, it is concluded that the major product from lithium aluminium hydride reduction of the olefin (107) is 4-Methylamino-2-phenylcycloheptene (123; 76% yield).



Scheme 37

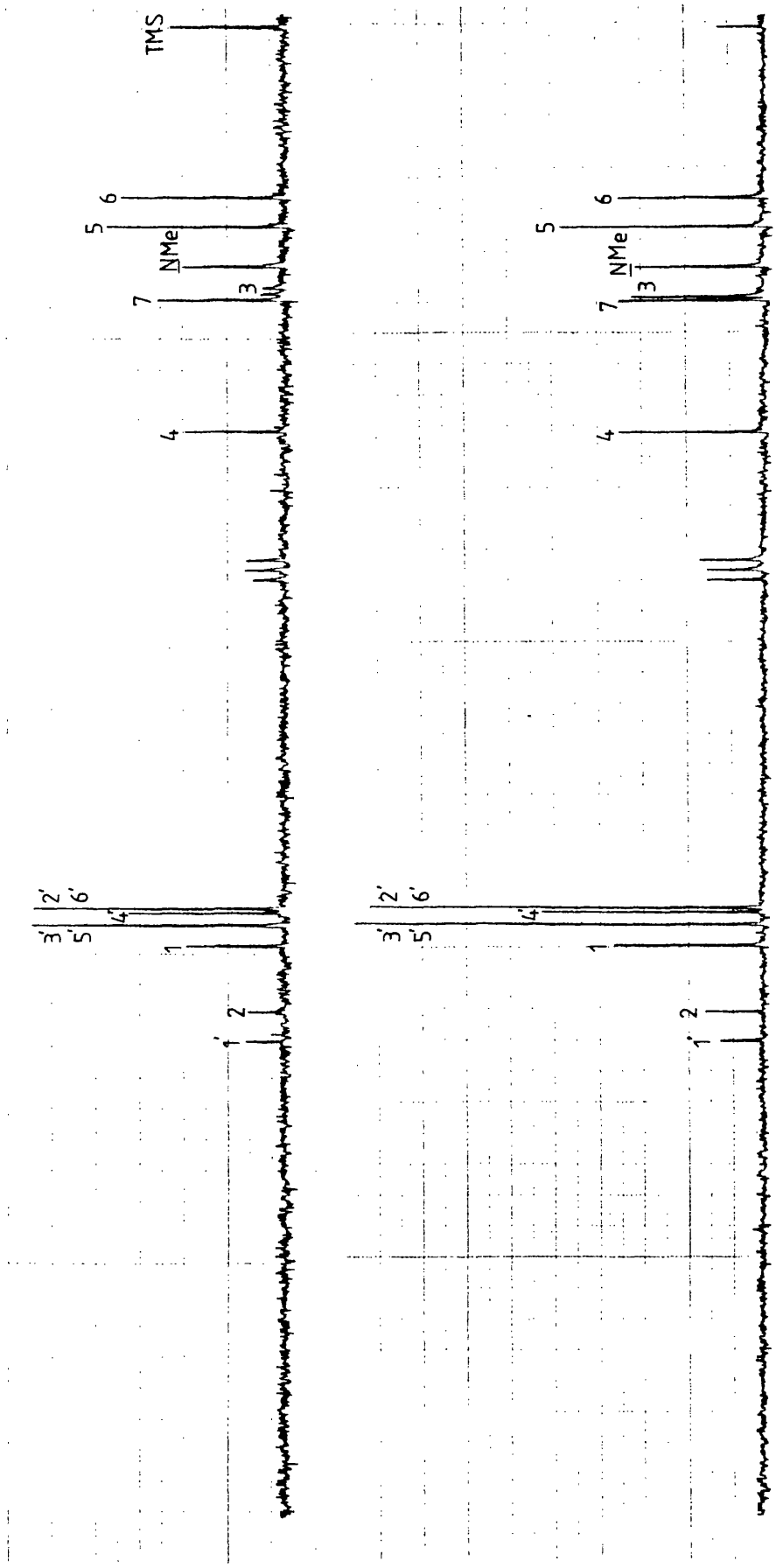


Fig. 21. ^{13}C NMR spectrum of 4-methylamino-2-phenylcycloheptene (123) in $CDCl_3$ (lower trace).

Fig. 22 ^{13}C NMR spectrum of 3-deutero-4-methylamino-2-phenylcycloheptene (125) in $CDCl_3$ (upper trace).

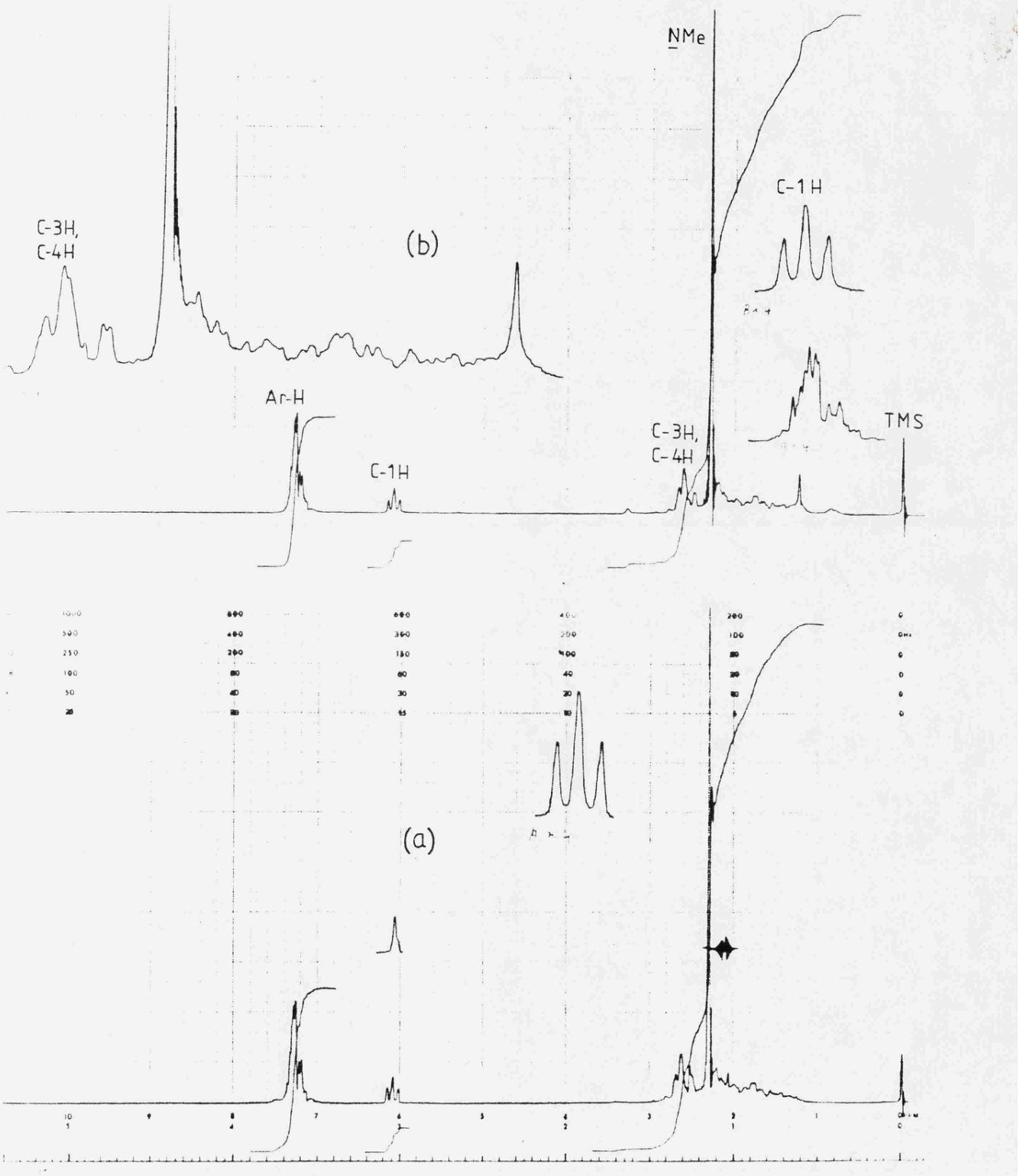


Fig. 23. ^{1}H NMR spectrum of 4-dimethylamino-2-phenylcycloheptene (127) in $CDCl_3$, (a) from Hofmann elimination of (126); (b) from N-methylation of (123).

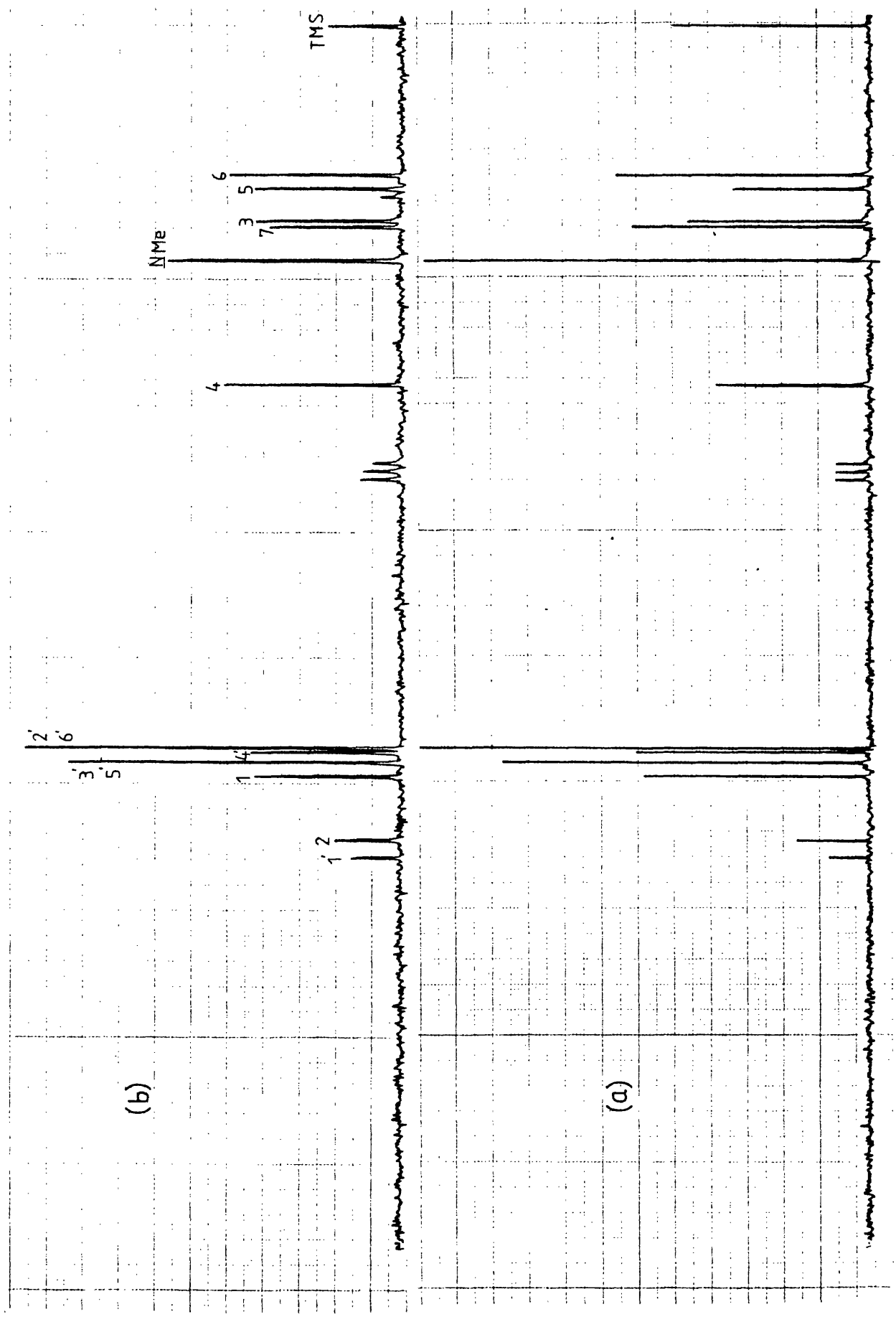


Fig. 24. ^{13}C NMR spectrum of 4-dimethylamino-2-phenylcycloheptene (127) in $CDCl_3$, (a) from Hofmann elimination of (126); (b) from N-methylation of (123).

The author envisages that thermodynamic, stereochemical and electronic factors are the driving forces of this ring opening reaction, a possible mechanism is presented in Scheme 36. Formation of a double bond between C-6 and C-7 of the highly deformed pyrrolidine ring[33] of the tropane framework has set the molecule(107) in a highly bond-angle strained condition[34,35]. Ring opening of the nitrogen bridge would relieve the intense bond strain developed and is hence a thermodynamically favourable process. Conjugation of the double bond with the aromatic ring results in a common delocalization of π electrons in both systems (see structure 111; Scheme 30). However, it is suggested that there may be some uneven distribution of the π cloud with slight deficiency in electrons at C-7 and relative enrichment of electrons in the aromatic ring. This would allow strong nucleophiles such as metallic hydrides to attack preferentially at the C-7 position.

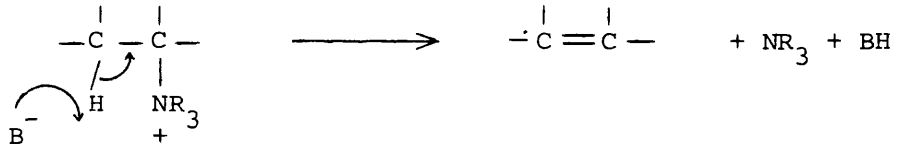
On the other hand, coordination[36] between the ring nitrogen of the olefin (107) and the aluminium atom of the metallic hydride would direct a specific exosteric attack of the hydride ion on C-7 of (107).

The net result of all these factors hence lead to a nucleophilic addition of the hydride ion on C-7, forcing the π electrons to centre on C-6. This carbanion intermediate (128) is stabilised by the electron withdrawing effect of the phenyl group. The next step involves the migration of the negative charge, formation of a double bond towards the bridgehead and subsequent ring opening of the nitrogen bridge. In the presence of a good coordination solvent[37] such as tetrahydrofuran, the aluminium atom coordinates with the solvent molecule instead of reacting with the carbanion

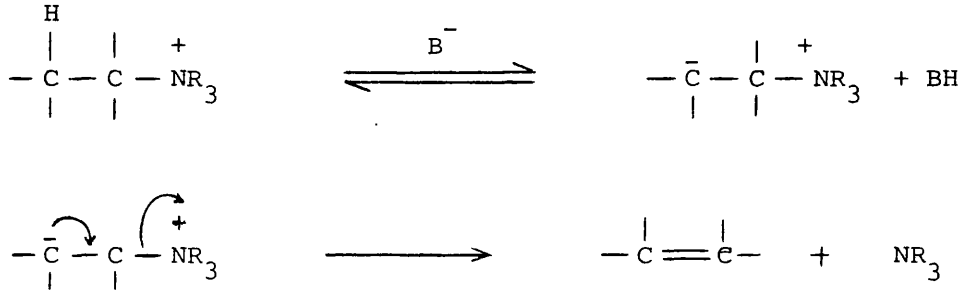
intermediate (128; see Scheme 36).

3.2.4 A cis-stereospecific Hofmann elimination of 6α-phenyl tropane methiodide[28]

The dichotomous nature of Hofmann elimination reactions was realized, extensively studied and discussed. These principles and investigations are in accord with the view that Hofmann elimination reaction of quaternary salts can proceed via either a synchronous E2-like mechanism[38-42] (Scheme 38; B^- = Base), or a stepwise ElcB-like process[43-45] (El elimination in the conjugation base; Scheme 39).

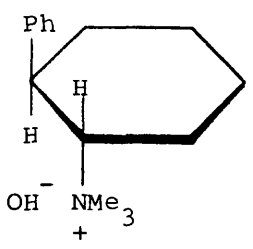


Scheme 38

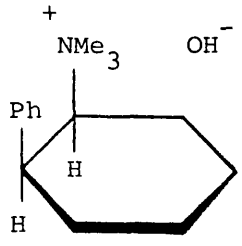


Scheme 39

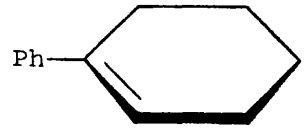
In many cases, the E2-like reaction shows a preference for trans-elimination[38-42]. This preference has been attributed to steric reasons, the suggestion being that in trans-elimination all three pairs of groups attached to C^{α} and C^{β} are in a staggered arrangement, whereas in the case of cis-elimination the corresponding three pairs of groups are nearly eclipsed[46]. Since in open-chain compounds, free rotation between the $C^{\alpha} - C^{\beta}$ bond would allow the molecule to adopt a number of conformations , cyclic systems, such as derivatives of cyclohexane have been employed to study the question of preference of trans- over cis-elimination. It was found that although both trans-2-phenylcyclohexyltrimethylammonium hydroxide (129) and the corresponding cis-isomer (130) underwent elimination to give 1-phenylcyclohexene (112), the reaction rate in the latter case is about 140 times faster[47-49]. Besides, since the cis-isomer (130) can adopt two conformations (Fig. 25, $-\underline{N}Me_3^+$ group in equatorial conformation and Fig. 26, $-\underline{N}Me_3^+$ group in axial conformation), it was suggested[50] that for facile elimination to take place, the $-\underline{N}Me_3^+$ group should have the axial conformation (FIg. 26) in the transition state so that the β-hydrogen will be axial, trans- and coplanar.



(129)



(130)



(112)

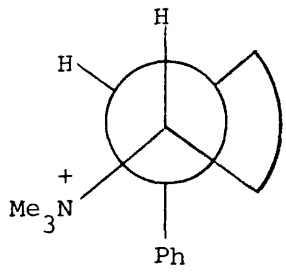


Fig. 25

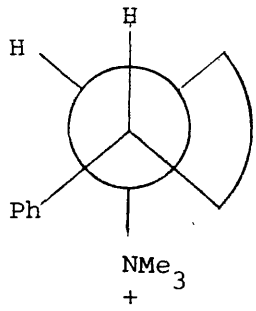
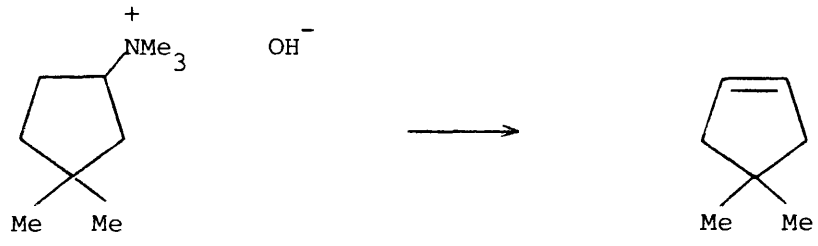


Fig. 26

The ElcB-like mechanism is exemplified by the pyrolysis of 3,3-dimethyl-cyclopentyltrimethylammonium hydroxide (131) to give 4,4-dimethylcyclopentene (Scheme 40).This reaction was found by deuterium labelling studies to proceed mainly via cis-elimination (76%)[51].



(131)

Scheme 40

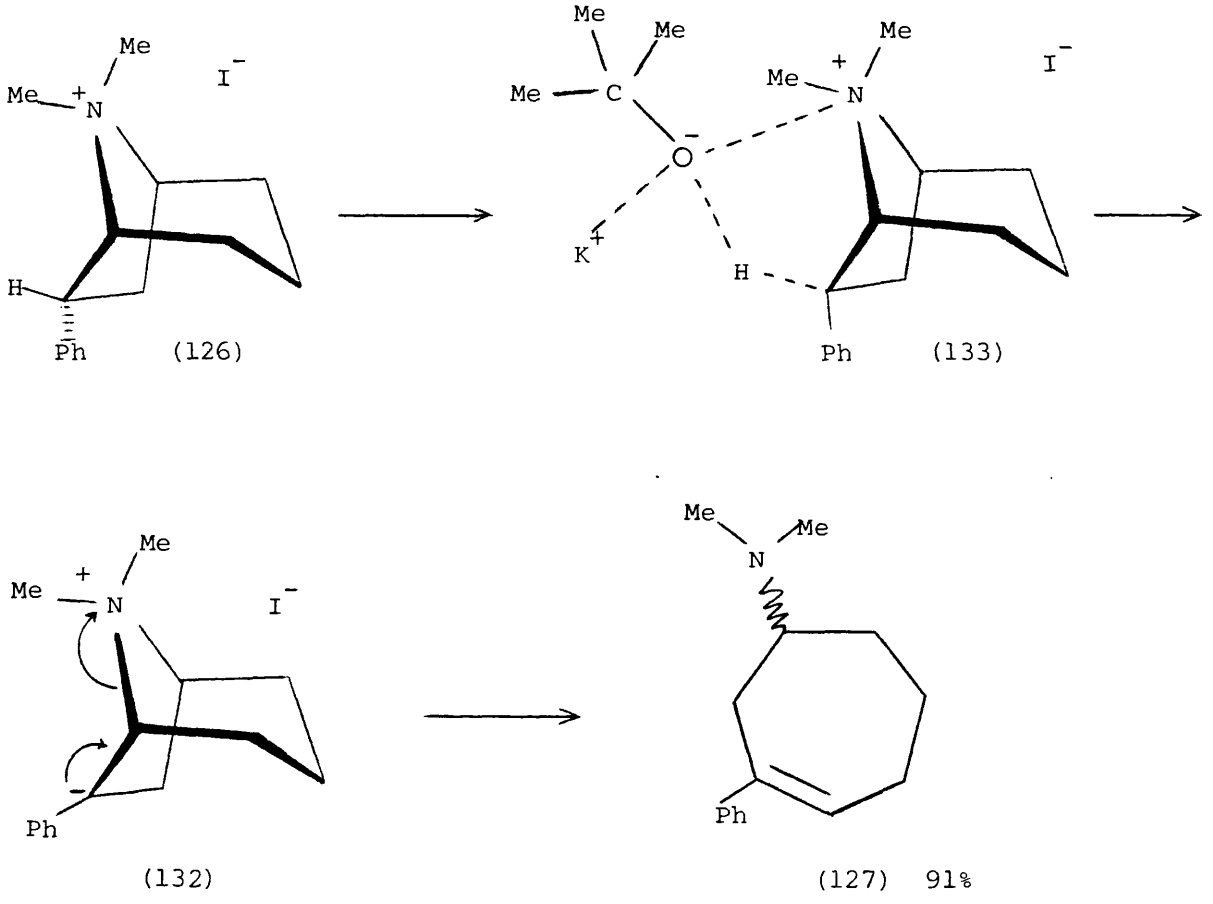
It has been considered[52] that there is a spectrum of mechanisms ranging from El-like to the ElcB-like. Between these two extremes is the E2-like mechanism, with synchronous departure of the β-proton and the leaving group.

Although trans-elimination predominates in many Hofmann elimination studies, cis-elimination processes can proceed in some cases without involving isomerization in the transition state[53]. However, cis-elimination of quaternary salts such as the trans-cyclohexyl compound (129) usually requires drastic conditions such as heating the quaternary salt in a sealed Pyrex tube at 106°C[53].

In this work the quaternary salt 6α-phenyltropane methiodide (126)[28] provides an interesting case for the study of cis-elimination because the quaternary function and the β-proton are in fixed orientations due to the frozen conformation of the 5-membered ring of tropane. Initially, it was considered that (126) might undergo elimination with great ease because of β-phenyl-activation[54,55]. This was soon proved not to be the case since refluxing the quaternary salt(126) in an aqueous 3.5N KOH solution failed to give any observable elimination reaction. However, it was found that this tropane quaternary salt (126) undergoes facile elimination to give the olefin (127) in a 91%yield after refluxing in an ethanolic solution of potassium tertiary butoxide (t-BuOK) for 2 - 3 days (Scheme 41.). This interesting experiment clearly demonstrates that cis-elimination is feasible.

The author envisages that this cis-stereospecific elimination proceeds via a ElcB mechanism[43] with the generation of a carbanion intermediate (132). The preference for this carbanion mechanism appears to be highly determined by the base strength of the reaction medium. This view is in accord with the observation that in many

systems studied an increase in the base strength causes an increase in the Hammett ρ-value [56-60], leading to the hypothesis[61-63] that the E2 transition state becomes more carbanionic towards the ElcB side as the base strength increases.



Scheme 41

The high yield of product in this cis-elimination suggests that certain crucial factors are responsible for enhancing the carbanion mechanism (ElcB-like process). This is attributed to a cyclic ion-pairing[64] between the quaternary salt (126) and the alkoxide ion in the transition state (Scheme 41). This cyclic intermediate (133) is suggested to promote an exosteric course in

the elimination of the β-proton. There is evidence[65] indicating that the basicity of dissociated t-BuOK is at least 10,000 times more than that of the ion-paired species. In cis-elimination reactions, the change from the associated to dissociated state of t-BuOK causes an increase in the Hammett ρ-value[66], suggesting an increase in the carbanion character of the transition state and hence approaching the ElcB side. Alternatively,this dramatic change in basicity of the associated alkoxide ion can be visualized as a transfer of negative ionic character from the base to the substrate in the ion-pairing transition state,thereby decreasing the basicity of the associated base itself. The nature of the solvent[67-69] is also considered to be crucial, possibly involving a stabilization of the ion-pairing complexes.

The carbanion intermediate (132) is stabilized by the -I inductive effect of the phenyl group. The remaining steps in Scheme 41 follow the same course as in the earlier ring opening mechanism described (Scheme 36), involving the formation of a double bond across C-5 and C-6, and forcing the nitrogen bridge to open.

3.2.5 Summary

The present investigations in this work suggest that in the reduction reactions (Scheme 33 and Scheme 36) and elimination reaction (Scheme 41) of 6-aryltropanes, the remarkable coordinating activity of the amino function with the various reagents (e.g. palladium charcoal, lithium aluminium hydride and potassium tertiary butoxide) is the major driving force which determines the steric course of the corresponding reaction. Even though the steric requirements of these

reagents are enormous, cyclic coordinating complexes[70,71] or ion-pairing[66] may operate at the transition state and direct a highly specific exosteric course of reaction. This suggestion is supported by the high percentage yield in all three reactions studied.

The exclusive exosteric course of these three reactions is further enhanced by the fact that steric hindrances at the exosteric side of tropane are considerably less than that at its endosteric side (see preceeding sections).

Solvent effects appear to operate *via* stabilization of the ionic transition intermediates, or by converting them into solvent-separated ion pairs[67-69]. The carbanion intermediates in Scheme 36 and Scheme 41 are considered to be stabilized by -I inductive effect of the β-phenyl group.

The fact that both mechanisms in Scheme 36 and Scheme 41 drive to a final ring opening process firmly support the argument that ring opening in tropanes is a thermodynamically favourable process. It is suggested that similar ring opening processes can be adopted by other bicyclic systems in which bond-angle strains are developed as a result of bridgehead effects.

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Part 4. Stereochemical studies of 6-substituted tropanes and their derivatives by ^{1}H and ^{13}C NMR spectroscopy

Extensive interest has been directed towards the ^{1}H NMR studies of 3-substituted tropanes[1-5]. However, only limited work has been carried out on ^{1}H NMR studies of 6-substituted tropanes[6]. On the other hand, ^{13}C NMR studies of 6-substituted tropanes have not been reported. The emphasis of this part has been laid on the stereochemical studies of a series of 6-substituted tropanes synthesized in this work, and the structural elucidation of some cycloheptene derivatives obtained from ring-opening reactions of 6-aryltropanes (see Part 3).

4.1 ^{1}H NMR studies

4.1.1 Proton Chemical Shifts

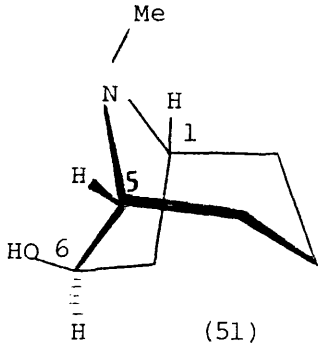
The proton chemical shift of 6-substituted tropanes are shown on Table 5. The most characteristic proton resonance is the N-Me signal which ranges from δ2.30 to δ2.64 for free bases and about δ3.2 for quaternary salts. The introduction of a substituent at the 6-position abolishes the symmetry of the tropane framework and thus produces magnetic non-equivalence between the C6-H and the C7-H as well as between the bridghead protons C1-H and C5-H. The C7-H frequently resonates as a multiplet in the range δ2.1 to δ2.9 for free bases and often overlapping with other signals. The 6-methine proton resonance, usually in the range δ4.0 -δ5.3, is useful for establishing the orientation of the 6-substituent (see Section 4.1.2). On the other hand, the C2-H, C3-H, and C4-H characteristically resonate upfield as multiplets with expected overlapping.

In 6β-substituted tropanes [exemplified by 6β-tropanol (51)], the bridgehead protons C1-H and C5-H are separated into signals

Table 5. 100 MHz ^{1}H NMR Chemical Shifts (δ_H) of 6-Substituted Tropanes (* From 60 MHz)

Compound	Solvent	N-Me or N-CH_2-	C1-H	C5-H	C6-H	C2-H, C3-H, C4-H and C7-H	CH_3-CO	O-Me	Ar-H
6β-Tropanol (51)	$CDCl_3$	2.49	2.93	3.24	4.26	0.94-2.13			
6β-Tropanol methiodide	DMSO-d_6	3.17} 3.27}	3.66	4.06	4.44	1.20-2.65			
*6β-Acetyloxytropane (136)	$CDCl_3$	2.47	3.07	3.27	5.10	0.87-2.31	2.02		
6β-Tropanol (106)	$CDCl_3$	2.39	3.00	3.00	4.57	1.00-2.10			
6α-Tropanol methiodide	DMSO-d_6	3.06} 3.19}	3.77	3.77	4.72	1.00-3.00			
*6α-Acetyloxytropane	$CDCl_3$	2.40	3.18	3.18	5.33	1.10-2.80	2.05		
6β-Hydroxytropinone (49)	$CDCl_3$	2.62	3.33	3.54	4.02	2.40-2.97(C7-H) 1.70-2.30(C2-H; C3-H; C4-H)			
*Tropane-6-one (52)	$CDCl_3$	2.38	2.91	3.46		1.05-2.60			
6β-Phenyl-6α-nortropanol (54)	DMSO-d_6		2.97	3.45		1.00-2.50			7.00-7.80
6β-Phenyl-6α-tropanol (53;R=H)	$CDCl_3$	2.47	3.25	3.06		0.84-2.80			7.00-7.70
6β-Phenyl-6α-tropanol methiodide (134)	DMSO-d_6	2.69} 3.24}	3.95	4.70		1.38-3.60			7.20-7.70
6β-Phenyl-6_-acetyloxytropane (53; R=Ac)	$CDCl_3$	2.50	3.27	3.64		0.84-2.92	2.05		7.00-7.60
6-Phenyl-6-tropene(107)	$CDCl_3$	2.30	3.52	3.76		6.20(C7-H); 1.00-2.10(C2-H; C4-H)			7.00-7.60
6α-Phenyltropane (120)	$CDCl_3$	2.64	3.34	3.34	3.86	0.87-2.68			7.00-7.60
6α-Phenyltropane methiodide (126)	DMSO-d_6	3.28} 3.28}	3.89-4.37	3.89-4.37	3.89-4.37	1.00-3.00			7.10-7.60
6β-(m-methoxyphenyl)-6α-acetyloxy-tropane (67; R = Ac)	$CDCl_3$	2.49	3.37	3.59		0.75-2.85	2.03	3.73	6.60-7.30
6β-(p-methoxyphenyl-6α-acetyloxytropane (68; R = Ac)	$CDCl_3$	2.47	3.23	3.58		0.79-2.90	2.03	3.74	6.60-7.40
6β-(m,p-dimethoxyphenyl)-6α-acetyloxytropane (66; R = Ac)	$CDCl_3$	2.52	3.28	3.65		0.90-2.93	2.06	3.85	6.60-7.20
N-Allyl-6β-phenyl-6α-acetyloxy-nortropane (62; R = Ac)	$CDCl_3$	3.42	3.35	3.68		0.90-2.95	2.07		7.00-7.50
*N-Cyclopropylmethyl-6β-phenyl-6α-acetyloxy-nortropane (61; R=Ac)	$CDCl_3$	2.64	3.43	3.86		1.00-2.60	2.05		7.00-7.70
*N-Phenethyl-6β-phenyl-6α-acetyloxy-nortropane (60; R=Ac)	$CDCl_3$	2.70	3.37	3.64		0.90-2.40	2.04		7.00-7.60
*N-(2-cyanoethyl-6β-phenyl-6α-acetyloxy-nortropane (56; R=Ac)	$CDCl_3$	3.00	3.42	3.42		0.90-2.50	2.08		7.10-7.70

readily distinguishable from one another. This is because the C5-H experiences significant magnetic anisotropic effects[1] from a vicinal 6β-substituent (dihedral angle between a 6β-substituent and C5-H ≒ 25°; Fig. 27).



(51)

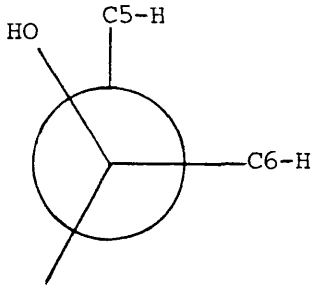
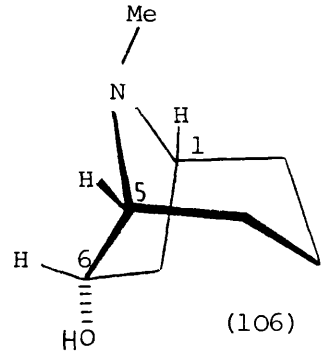


Fig. 27



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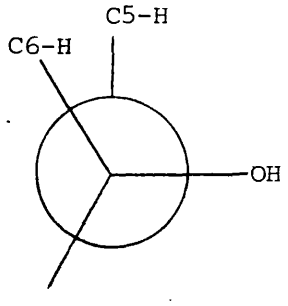


Fig. 28

However, in 6α-substituted tropanes [exemplified by 6α-tropanol (106)], the dihedral angle between a 6α-substituent and C5-H ≒ 85°, (Fig. 28), thereby reducing magnetic anisotropic effects on the C5-H. As a result, 6α-substituted tropanes usually show bridgehead signals as overlapping multiplets (see Table 5).

Very significant deshielding effects are experienced by the C-6 protons of (51) and (106) on acetylation ($\Delta\delta$ = 0.84 and 0.76 p.p.m. respectively). Acetylation of the 6-hydroxyl group produces a slight deshielding effect on the bridgehead proton C5-H of 6β- and 6α-tropanols and a significant downfield shift of the C5-H

of 6β-phenyl-6α-tropanol (53; R = H; $\Delta\delta$ = 0.58 p.p.m.).

For (53; R = H), there has been some speculation[6] as to whether the broader signal at δ3.25 (peak base width at half the maximum height[7] $W_{\frac{1}{2}}$ = 6.8 Hz) or the signal at δ3.06 ($W_{\frac{1}{2}}$ = 3.5 Hz) corresponds to C5-H or C1-H respectively, or *vice versa* (see Fig. 29a). It was originally thought that the signal at δ3.25 and δ3.06 corresponded to C5-H and C1-H respectively, from a consideration of the deshielding effect of the 6-substituents on the vicinal C5-H. However, the ^{1}H NMR spectrum of the methiodide (134) shows that one of the proton signals is deshielded to δ4.7 ($W_{\frac{1}{2}}$ = 2.5 Hz) whereas the broader signal resonates at δ3.95 ($W_{\frac{1}{2}}$ = 7.4 Hz), (Fig. 29b). Since quaternization deshields both proton signals, there is insufficient information at this stage to make definite chemical shift assignments to C1-H and C5-H of (53; R = H). However, acetylation of the 6-hydroxyl groups of (53; R = H) causes the sharper proton signal to shift to a lower field resonance of δ3.64 ($W_{\frac{1}{2}}$ = 3.5 Hz), whereas resonance of the broader signal stays at δ3.27 ($W_{\frac{1}{2}}$ = 6.8 Hz), (Fig. 29c). These data support the alternate assignment of the proton resonances at δ3.25 ($W_{\frac{1}{2}}$ = 6.8 Hz) and at δ3.06 ($W_{\frac{1}{2}}$ = 3.5 Hz) to C1-H and C5-H of (53; R = H) respectively, since acetylation of the 6-hydroxyl group would produce a greater change of chemical shift of the vicinal C5-H than a more remote C1-H. Similar assignments are applied to the C1-H and C5-H resonances of other 6β-aryltropanes.

It is suggested that in 6β-aryltropanes [exemplified by (53; R = H)], the aryl ring is in an orientation (see Fig. 30) such that the vicinal C5-H experiences an anisotropic shielding effect. However,

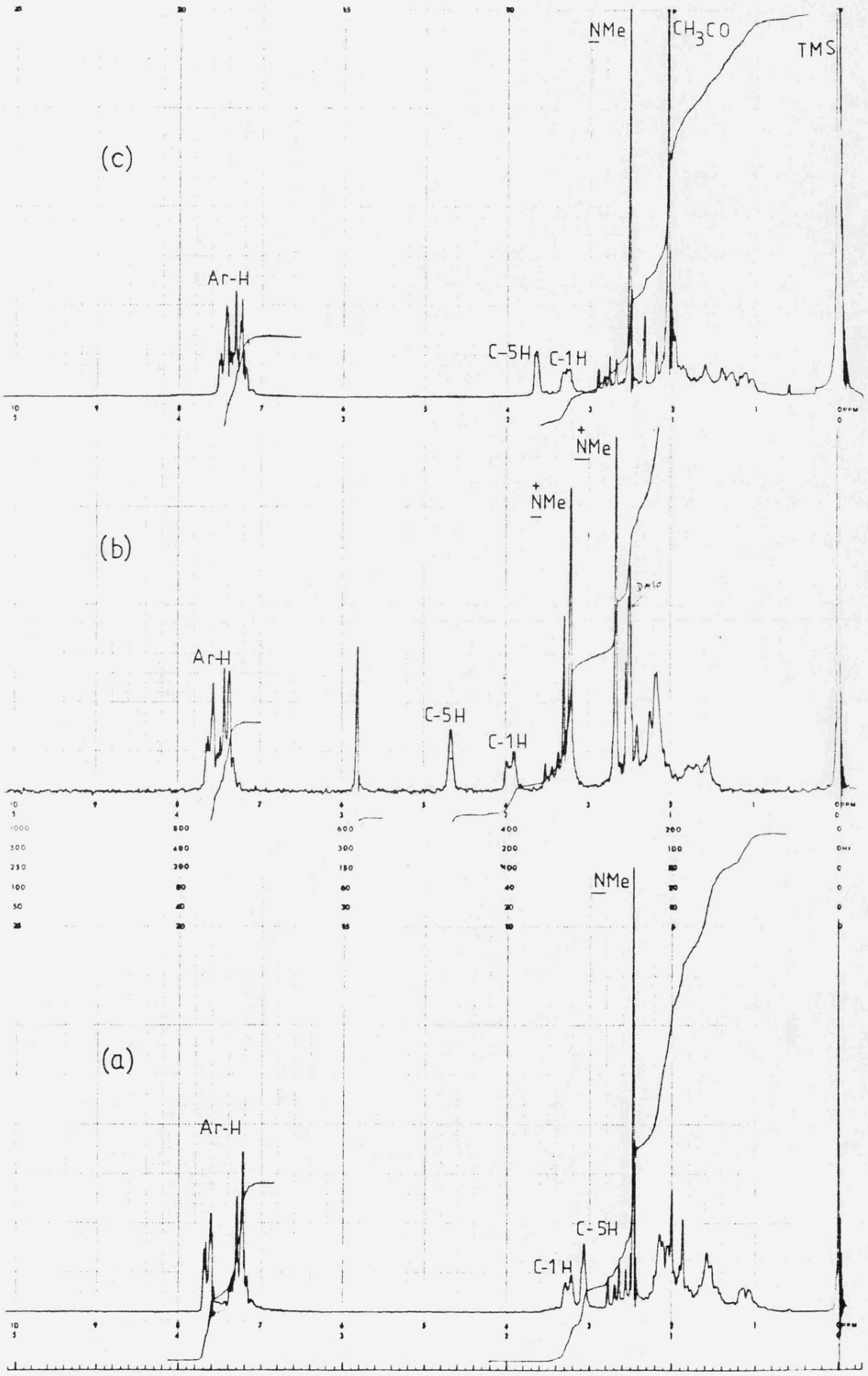
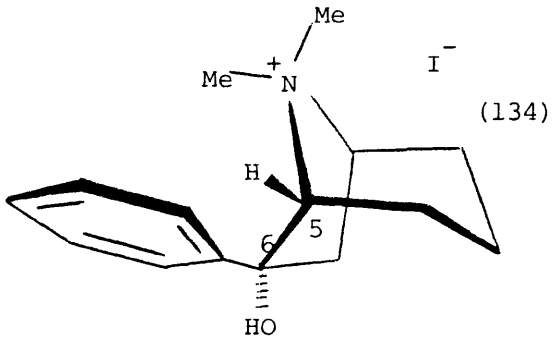


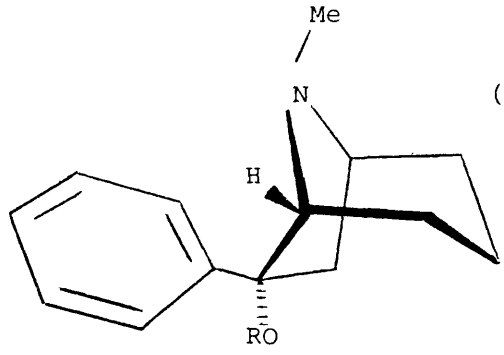
Fig. 29. ^{1}H NMR spectrum, (a) 6β-phenyl-6α-tropanol in $CDCl_3$; (b) 6β-phenyl-6α-tropanol methiodide in DMSO-d_6; (c) 6β-phenyl-6α-acetyloxytropane in $CDCl_3$.

quaternization of the tertiary alcohol changes this spatial orientation of the aryl ring (Fig. 31) so that deshielding anisotropy in turn operates on C5-H.



(134)

Fig. 31



(53)

Fig. 30

4.1.2 Configurational studies and structure elucidation.

^{1}H NMR is considered to be particularly useful in the configurational studies of 6-substituted tropanes. The configuration of the 6-hydroxyl group of 6β-tropanol (51) and 6α-tropanol (106) was established[6] by a consideration of vicinal coupling constants between C6-H and C5-H, according to the Karplus $\cos^2\phi/J$ relationship[8].

The determination of the configuration of the aryl ring in 6β-aryltropanols comes from ^{1}H NMR studies of the tertiary base (53; R = H) and its methiodide[6, 9]. It is observed that one $\overset{+}{N}$-Me signal of the methiodide (134) resonates at an unusually high field position of δ2.69, indicating that the equatorial $\overset{+}{N}$-Me group must experience strong anisotropic shielding effects from the aromatic ring (Fig. 30), indicating a β-orientation of the aryl group.

For the determination of the 6-phenyl configuration of the

product resulting from hydrogenation of the olefin (107) in this work (Part 3; P. 112), the same principle is employed. The reduction product (120) has its N-Me signal resonating at δ2.64 (Fig. 32a) whereas the two $\overset{+}{N}$-Me groups of the corresponding methiodide (126) overlap as a singlet at δ3.28 (Fig. 32b). There is no observable anisotropic effect of the phenyl group operating on the equatorial $\overset{+}{N}$-Me group and this would indicate an α-orientation of the phenyl group[10]. The methine proton C-6 of (120) also appears as a broad multiplet ($W_{\frac{1}{2}} \doteqdot 27$ Hz), suggesting that large vicinal coupling operates between C6-H and C5-H, thereby indicating a β-orientation of the C6-H and hence an α-orientation of the phenyl group. The bridgehead protons C1-H and C5-H also overlap as a multiplet at δ3.86 (Fig. 32a) showing that the C5-H is free from anisotropic effects of the phenyl ring. All data concur with an α-orientation of the aromatic ring in (120).

The structure elucidation of an unknown major product (123) from lithium aluminium hydride reduction of 6-phenyl-6-tropene has been described in detail in Part 3[10]. The proton resonances of the three cycloheptene derivatives are listed in Table 6. The most important information from these ^{1}H NMR spectra is the retention of the C-4 olefinic proton triplet (δ6.13) in the spectrum of the deuterated compound (125), indicating the steric course of attack by the deutero-hydride ion. Another important aspect is that the intensity of the C2-H resonance in the deuterated compound is half that of the corresponding C2-H (2H) in (123). The data support the proposed mechanism (Scheme 36) and the structure (123; Part 3).

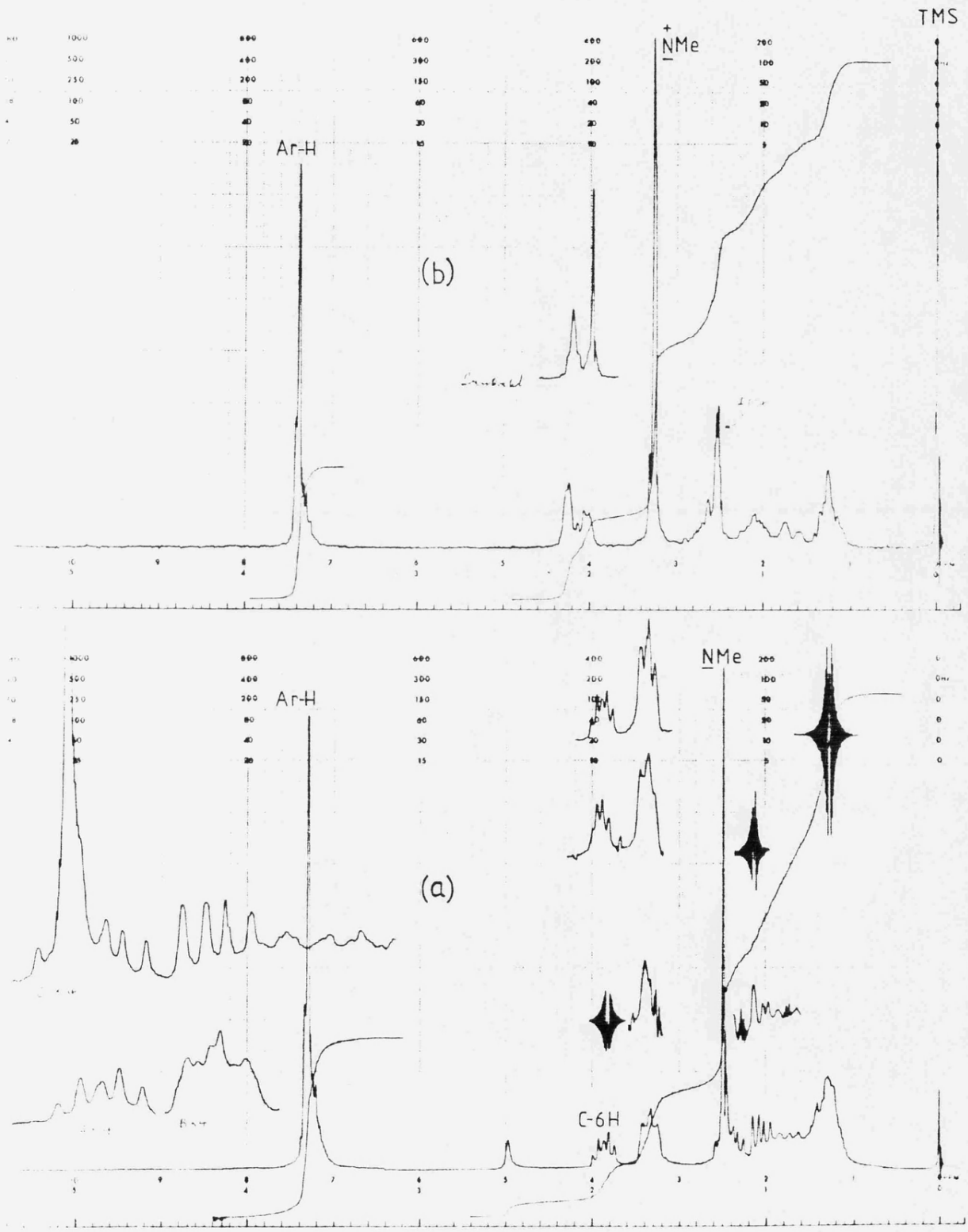
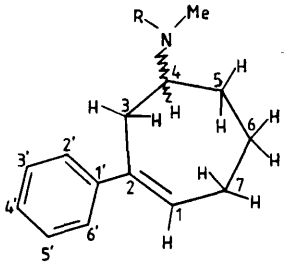


Fig. 32. ^{1}H NMR spectrum, (a) 6α-phenyltropane (120) in $CDCl_3$; (b) 6α-phenylmethiodide (126) in DMSO-d_6

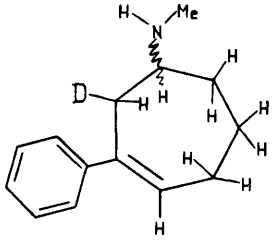
Table 6. ^{1}H NMR Chemical Shifts (δ_H) of Some Products from Ring-Opening Reactions of 6-Substituted Tropanes

Compound	Solvent	N-Me	C1-H	C3-H	C4-H	C5-H, C6-H	C7-H	Ar-H
4-Methylamino-2-phenylcycloheptene (123)	$CDCl_3$	2.42	6.13	2.69	2.54	1.00-2.40	~1.96	6.90-7.60
4-Dimethylamino-2-phenylcycloheptene (127)	$CDCl_3$	2.32	6.12	2.64	2.50	1.10-2.20	~2.10	7.00-7.60
3-Deutero-4-methylamino-2-phenylcycloheptene (125)	$CDCl_3$	2.42	6.13	2.72	2.57	1.00-2.40	~2.20	6.90-7.60



(123) : R = H

(127) : R = Me



(125)

Table 9. ^{13}C NMR Chemical Shifts (δ_C) of Some Products from Ring-Opening Reactions of 6-Substituted Tropanes

	Solvent	N-Me	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Aromatic moiety C-1'	C-4'	C-2',C-6'	C-3',C-5'
4-Methylamino-2-phenylcycloheptene (123)	$CDCl_3$	34.1	131.1	140.6	38.3	57.5	28.4	24.3	38.8	144.8	126.4	125.7	128.2
4-Dimethylamino-2-phenylcycloheptene (127)	$CDCl_3$	40.7	130.6	141.7	34.0	62.2	28.4	26.0	34.9	144.7	126.4	125.7	128.2
3-Deutero-4-methylamino-2-phenylcycloheptene (125)	$CDCl_3$	34.1	131.2	140.6	38.2	57.4	28.5	24.3	38.7	144.9	126.4	125.8	128.2

4.2 ^{13}C NMR studies

4.2.1 Introduction

The growing importance of ^{13}C NMR spectroscopy in the structural and stereochemical investigation of organic molecules is generally recognized by chemists today. The development of pulse and Fourier-transform techniques[11,12] allied with mini computers has made the quality of ^{13}C NMR studies comparable to that of ^{1}H NMR, despite the low natural occurrence (1.1%) of the ^{13}C nuclei.

The distinct advantage of ^{13}C NMR is that it allows a direct observation of the molecular carbon backbones of complex organic molecules. The fine structure of the peaks as a result of ^{1}H-decoupling is useful for chemical shift assignments, as well as for lanthanide-induced ^{13}C NMR shift studies[13] (see Section 4.3). The striking dependence of chemical shifts on molecular geometry and substitution also makes ^{13}C NMR spectroscopy a very important structural tool in the determination of stereochemistry[14].

In general, an alkyl substituent in the α- or β- position deshields the carbon nucleus but a γ-substituent has a shielding effect[15]. These long range effects (γ-, δ-,and ε-) are relatively small in acyclic compounds. but may be quite significant in cyclic systems. Theoretical interpretations of these observations have been advanced[16,17]. However, in bicyclic or fused ring compounds, theoretical explanations become rather complicated and an empirical approach serves better in structural and stereochemical investigations.

The influence of heteroatoms on ^{13}C chemical shifts have been

considered as arising from alterations in the electron density at carbon caused by variations in the electronegativity of the heteroatom[18,19]. The α-shift has been shown to be a function of the electronegativity of the heteroatom X. Methyl substitution at the heteroatom causes a downfield shift at the α-carbon. The presence of a heteroatom produces a marked upfield shift of the γ-carbon atom (Fig. 33). Grant and Cheney[20] suggested that the mechanism for the shielding effect of a carbon by a γ-gauche substituent is steric polarization of the valence electrons, whereas that by an α substitution is charge polarization.

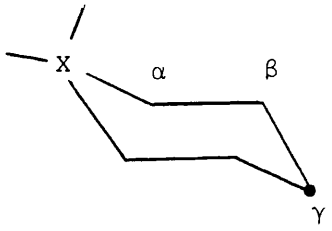


Fig. 33

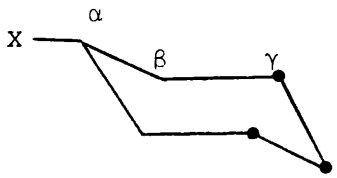


Fig. 34

The γ effect is complicated further by the influence of a substituent at X (such as methyl) which, when axial, produces a substantial upfield shift of the β -carbon.However, this effect is virtually absent when the 1-substituent is equatorial[21]. Lambert et al.[19] pointed out that the substituent-induced γ effect (steric shift)of the 1-methyl group on the β-carbon should be a useful predictor of the conformational preference of the methyl group.

The γ-anti effect was first proposed by Eliel et al.[22] who originally considered that the effect was upfield shifting for

second-row heteroatoms (O, N, F). This effect was found to vanish or was reversed (downfield shift) when the heteroatom was attached to the bridgehead atom in a bicyclic system. It was further suggested[23,24] that the downfield effect of γ-anti shifts arises from the high degree of substitution around the bridgehead, and not from the bridgehead position of the electronegative substituent.

The symmetry-induced structural characteristics of 3-substituted tropanes made the assignment of the carbon atoms almost trivial[26]. However, the lack of symmetry in the 6-substituted tropanes make chemical shift assignemtns rather more difficult. The author found that application of chemical shift theories and empirical correlations was useful in the analysis of rather complicated ^{13}C NMR spetra obtained in this work. Examination of the multiplicities in the off-resonance spectrum also facilitates the assignment of the noise decoupled spectra.

4.2.2 ^{13}C NMR spectral characteristics and stereochemical investigation of 6-substituted tropanes and their derivatives.

(a) Chemical shifts of aliphatic carbons

The ^{13}C NMR chemical shifts of a series of 6-substituted tropanes prepared by the author are listed in Table 7 and the corresponding chemical shift correlations showing assignments and substituent effects are expressed in Fig. 35. The substituent parameters are shown in Table 8. The significant deshielding effect at the α- and β-carbons is apparently related to the electron-withdrawing ability of the substituent. However, it appears that configurational

Table 7. ^{13}C NMR Chemical Shifts (δ_C) of 6-Substituted Tropanes

Compound	Solvent	N-Me or N-CH_2-	C-3	C-2	C-4	C-1	C-5	C-6	C-7	CH_3-C(=O)-O	CH_3-CO	Aromatic Moiety C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	O-Me
6β-Tropanol (51)	$CDCl_3$	36.8	17.2	25.2	23.7	60.5	68.5	76.0	40.4									
6β-Acetyloxytropane (136)	$CDCl_3$	38.6	17.2	27.1	25.5	61.1	66.4	79.1	36.4	170.8	21.3							
6α-Tropanol (106)	$CDCl_3$	37.4	17.0	26.3	21.3	59.3	63.0	71.6	37.2									
6α-Acetyloxytropane	$CDCl_3$	38.8	16.9	28.0	23.5	59.4	61.4	74.9	33.5	170.8	21.0							
6β-Hydroxytropinone(49)	$CDCl_3$	35.2	207.9	41.7	41.4	59.4	68.5	75.3	43.9									
Tropan-6-one (52)	$CDCl_3$	40.4	16.7	28.3	26.6	58.7	68.2	219.1	38.2									
6β-Phenyl-6α-tropanol (53; R = H)	$CDCl_3$	34.1	17.4	21.9	18.4	58.5	67.6	80.9	47.2			151.3	125.0	128.0	126.4	128.0	125.0	
	DMSO-d_6	33.5	17.1	21.2	17.6	57.7	67.9	79.1	47.4			152.9	125.2	127.2	125.5	127.2	125.2	
6β-Phenyl-6α-acetyloxy-tropane (53; R = Ac)	$CDCl_3$	33.8	17.7	21.7	18.4	57.6	65.8	87.8	44.9	169.8	21.7	147.5	124.7	128.0	126.4	128.0	124.7	
6β-Phenyl-6α-nortropanol (54)	DMSO-d_6		17.7	32.4	28.6	54.0	64.0	80.8	45.9			152.3	125.1	127.3	125.5	127.3	125.1	
6-Phenyl-6-tropene (107)	$CDCl_3$	42.2	16.5	25.6	25.6	68.5	68.5	134.9	123.5			140.6	126.0	128.6	127.4	128.6	126.0	
6α-Phenyltropane (120)	$CDCl_3$	40.1	16.0	28.8	25.4	61.2	65.3	43.8	30.2			141.2	128.0	128.2	125.5	128.2	128.0	
N-Cyclopropylmethyl-6β-phenyl-6α- nortropanol (61; R=H).	$CDCl_3$	51.4	17.6	22.1	18.4	57.1	65.6	80.5	47.4			151.7	125.0	127.9	126.3	127.9	125.0	
6β-(m-methoxyphenyl)-6α-acetyloxytropane(67;R=Ac)	$CDCl_3$	33.7	17.7	21.6	18.3	57.3	65.6	87.6	45.0	169.9	21.7	149.2	111.1	159.4	111.5	128.9	117.1	55.0
6β-(m,p-dimethoxyphenyl)-6α-acetyloxytropane (66;R=Ac)	$CDCl_3$	34.0	17.7	21.7	18.6	57.5	65.9	87.9	44.9	170.0	21.9	140.3	109.4	147.8	148.8	111.0	117.2	55.9
N-Allyl-6β-phenyl-6α-acetyl-oxy-nortropane (62;R=Ac)	$CDCl_3$	49.8	17.5	22.2	18.9	55.9	63.7	87.5	44.4	169.8	21.6	147.4	124.8	127.9	126.3	127.9	124.8	
6β-(p-methoxyphenyl)-6α-tropanol (68; R = H)	$CDCl_3$	34.4	17.5	22.2	18.6	58.7	67.8	80.7	47.0			143.7	126.3	113.4	158.3	113.4	126.3	55.3

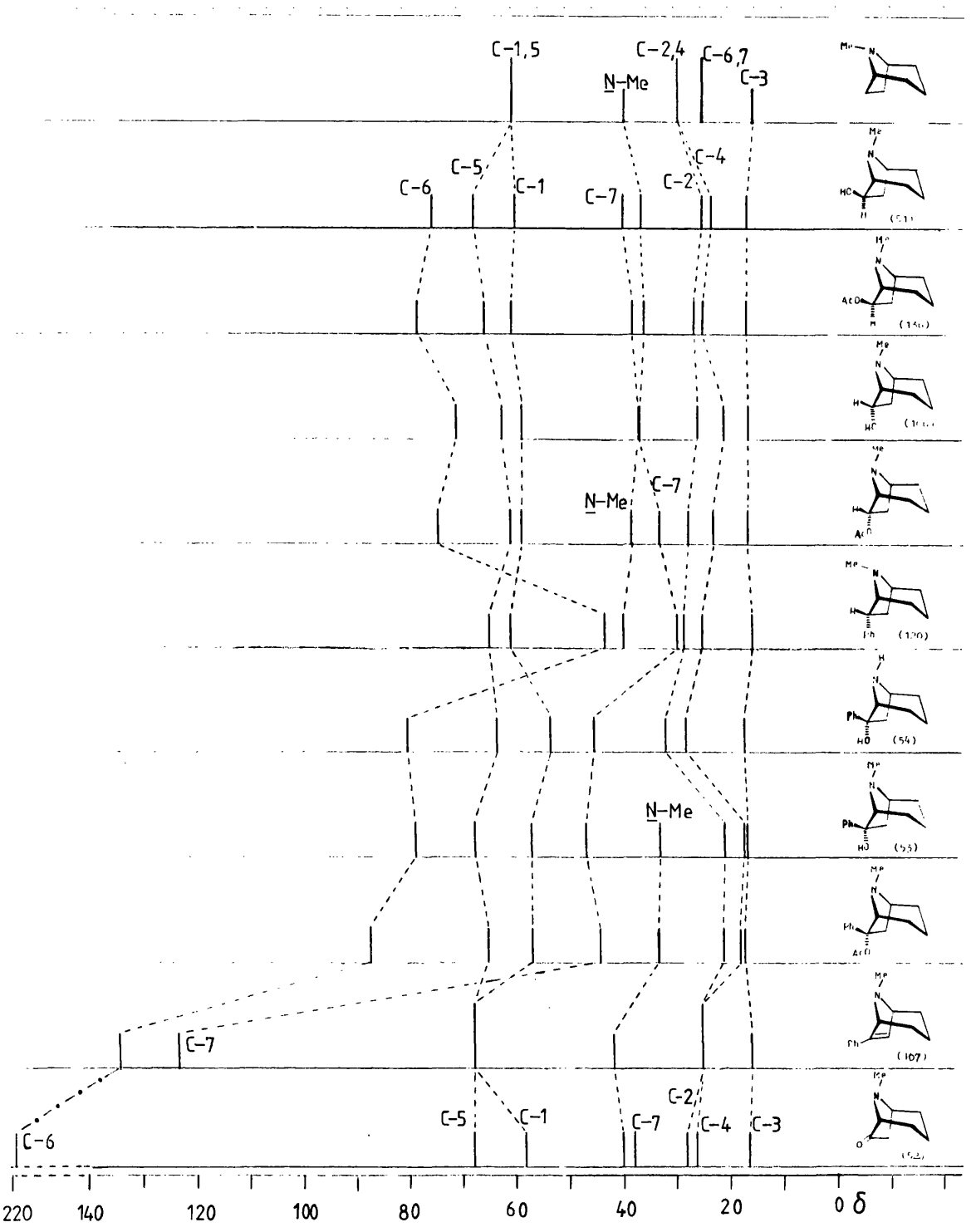


Fig. 35. ^{13}C NMR chemical shift correlations of a series of 6-substituted tropanes.

differences have marked influences on these substituent effects. For example, the C-6 resonance of 6β-tropanol is 4.4 p.p.m more downfield that that of 6α-tropanol.@ In addition, the C-5 resonance of 6β-tropanol is 5.6 p.p.m. more downfield than that of its isomer, indicating an apparent difference in the operation of the β-effect by the same heteroatom (oxygen). α- and β- effects are considered to arise through bond effects[27,28]. However, in the case of 6-substituted tropanes, these direct bond effects are complicated by other stereochemical parameters. It is envisaged that the substitution of a β-hydroxyl group at the 6-position of tropane causes enhanced steric crowding at the bridghead position, causing electron orbital contraction[40] of C-5, resulting in a downfield shift of the C-5 resonance. The contraction of orbital dimensions was proposed as a means of reducing unfavourable steric interactions[40].

Table 8. ^{13}C substituent parameters ($\Delta\delta_C$) of 6-substituted tropanes

Substituent	α(C-6)	β(C-7)	γ(C-4)
-OH*	46.0	11.6	-4.3
-OAc **	3.3	-3.7	2.2
=O$^{\Delta}$	193.5	12.6	1.0
-Ph^{++}	18.2	4.6	-0.2
β-Ph; α-OH§	51.8	16.9	-4.3

* Measured from chemical shifts of 6α-tropanol (106) and relative to tropane[29].

** Measured from chemical shifts of 6α-acetyloxytropane and relative to 6α-tropanol.

Δ Measured from chemical shifts of tropan-6-one (52) and relative to tropane.

++ Measured from chemical shifts of 6α-phenyltropane (120) and relative to tropane.

§ Measured from chemical shifts of 6β-phenyl-6α-nortropanol (54) and relative to nortropane[29].

@Intramolecular H-bonding between the β-hydroxy function and ring nitrogen in 6β-tropanol may account for this chemical shift difference.

As shown in Table 8, a sp^2 oxygen substituent[30] has the strongest deshielding α-effect whereas a disubstituent (β-phenyl, α-hydroxy) has the strongest β-effect. A phenyl substituent has the least α- and β- effect in the four substituent parameters studied. Most substituents listed in Table 8 have a shielding effect on the γ-carbon. However, the carbonyl oxygen appeared to have a slight deshielding effect on the γ-carbon ($\Delta\delta_C$ = 1.0 p.p.m.). Acetylation produces a significant downfield shift of the α-carbon and upfield shift of the β-carbon, while causing the γ-carbon to be deshielded (for 6α- and 6β-tropanol acetates). For the tertiary alcohol (53; R = H), acetylation causes a significant downfield shift of the α-carbon ($\Delta\delta_C$ = 8.7 p.p.m.) and upfield shift of the β-carbon ($\Delta\delta_C$ = -2.5 p.p.m) whereas little change is observed for the chemical shift of the γ-carbon (see Fig. 35).

The olefin 6-phenyl-6-tropene (107) has rather unique chemical shifts. The high downfield resonance of C-6 (δ134.9) and C-5 (δ 123.5) are characteristic of substituted olefins[31-33]. It has been suggested (see Part 3) that the double bond of (107) is strongly conjugated with the aromatic ring. Despite the 6-phenyl substituents the olefinic bond appears to exert equal β-effects on C-1 and C-5 and equal γ-effects on C-2 and C-4 respectively. As a result, C-1 and C-5 resonances emerge as a singlet at δ68.5 whereas the C-2 and C-4 resonances overlap at δ25.6 (see Table 7).

The assignment of the aliphatic carbons (Table 9) in the seven-membered ring products from the ring-opening reactions (see Part 3) follows the same approach used in the 6-substituted tropanes. The

most upfield signals are assigned to C-5 and C-6. The olefinic carbons C-1 and C-2 occur at the substituted double bond resonance region of about δ141 and δ131 respectively. Although the resonances of C-3 and C-7 are very close, precise assignment can be made by referring to the 3-deutero compound (125) in which the C-3 signal appears as a triplet centred at δ38.2.

(b) Chemical shifts of aromatic moiety

Theoretical studies of aromatic ^{13}C chemical shifts have been advanced[52, 58]. It has been suggested[59-61] that no general relationship between ^{13}C chemical shifts and local electron density exists. However, in a special case of benzene carbon para to a substituent, there is certain correlation between total charge density and ^{13}C chemical shifts[62]. Factors such as steric, inductive and field effects are also considered to affect ortho and meta ^{13}C shifts[63]. In addition, substituent effects for aromatic ^{13}C are remarkably additive.

The ^{13}C aromatic region in 6-aryltropanes is assigned with the aid of chemical shift parameters of mono-substituted benzenes[43]. For a mono-substituted phenyl group (for example, in 6β-phenyl-6α-tropanol), the C-1' appeared to be the most deshielded carbon whereas the para carbon (C-4') is slightly shielded. Carbons at the ortho positions (C-2' and C-6') occur upfield of these at meta (C-3' and C-5'). Substitution of electron donating groups such as O-Me group in the aromatic ring markedly deshields the substituted carbon, while causing the vicinal carbons (ortho) and the para carbon to shift upfield (see Table 7).

(c) Diamagnetic shifts induced by steric polarization of N-substituents

The N-configuration of tropanes has been a topic of much discussion[34-37] (see General Introduction). X-ray crystallographic studies[36,37] indicate that in the solid state, the N-Me group of 3-substituted tropanes is equatorially orientated. This may indicate that the equatorial side of 3-substituted tropanes is the more sterically favourable side[34]. The determination of the N-configuration of 6-substituted tropanes has not yet been reported.

In this work, the N-configuration of 6-substituted tropanes is determined by the application of the theory of steric polarization of the valence electrons in the molecule[38-42]. It was proposed[40,42] that an induced polarization of charge along the H-C bond is accompanied with an increase in electron charge density, causing upfield steric shifts. Examination of the ^{13}C chemical shifts of 6β-phenyl-6α-tropanol (53; R = H) and the secondary amine (54) shows that the C-2 and C-4 resonances of the tertiary base are considerable more upfield than those in the secondary amine (54). The $\Delta\delta$ values are 10.5 p.p.m. and 10.1 p.p.m. for C-2 and C-4 respectively. The author envisages that an axial N-Me group in (53; R = H) would exert certain steric polarization effects on the H-C bond of C-2 and C-4, causing an electron expansion[42] about the nucleus and resulting in an upfield shift of the resonance position (Fig. 36). In the secondary amine (54), the absence of the N-Me group allows C-2 and C-4 to be free of steric polarization effects. Further evidence comes from other N-substituted 6β-aryltropanes such as (61; R = H) and (62; R = acetyl), in which the C-2 and C-4 also experience similar steric shifts.

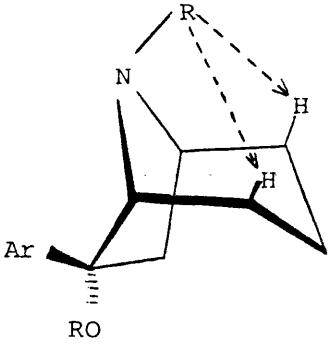


Fig. 36

These results imply a preference for the axial N-configuration in the 6β-aryltropanes. It is considered that this axial N-configuration would preclude unfavourable steric interaction between the N-Me group and the β-phenyl group.

For the secondary alcohols 6β-tropanol and 6α-tropanol, the steric polarization effect is not so pronounced as in the 6β-aryltropanes. This may imply that in an apolar solvent such as $CDCl_3$, there is equilibrium of both axial and equatorial forms in solution.

The fact that the C-2, C-4 resonances of 6α-phenyltropane (120) are more downfield than that of the 6β-aryltropanes suggests that the N-Me group of (120) may also exist in an axial-equatorial configurational equilibrium[35], with higher preference for the sterically more favourable equatorial N-configuration.

4.3 Qualitative determination of enantiomeric purity of resolved 6β-tropanols by ^1H and ^{13}C NMR using a chiral shift reagent.

The phenomenon of enantiomeric nonequivalence in a dissymmetrical environment (e.g. chiral solvent), detectable by NMR spectroscopy,

was first observed by Pirkle[44]. Hinckley[45] further demonstrated that lanthanide chelates induce chemical shift differences between isomers in NMR spectra. This lanthanide induce shift (LIS) phenomenon is considered to be the result of the formation of a complex between the ligand and a coordinately unsaturated lanthanide shift reagent.

It was observed[46,47] that a chiral shift reagent C* will produce a differential shift ($\Delta\Delta\delta$) between an enantiomeric pair (R, S) distinguishable by NMR.

$$C^* + R \rightleftharpoons (C^*R)$$

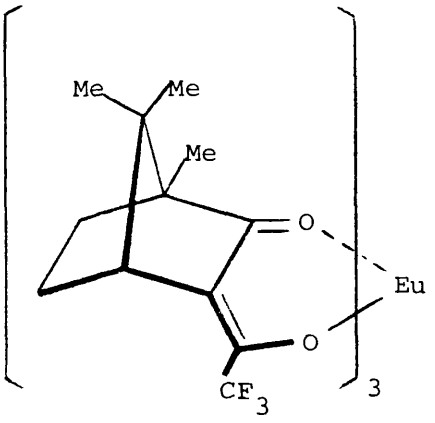
$$C^* + S \rightleftharpoons (C^*S)$$

Since the association and dissociation of the shift reagent and the ligands is a fast equilibrium process, it is expected that induced paramagnetic shifts ($\Delta\delta$) and the differential shift ($\Delta\Delta\delta$) between the diastereoisomeric adducts C*R and C*S are dependent on the molar ratio of shift reagent to ligand[57]. However, when the shift reagent concentration reaches a certain upper limit, then the substrate shift is independent of lanthanide concentration[48].

In this work, the enantiomers (+)- and (-)- 6β-tropanol obtained by resolution (see Part 2) have the rather small specific rotation values of +2.4 and -2.3 respectively. Although these values are opposite in sign and essentially equal, it is necessary, and of interest, to determine the enantiomeric purity of these isolated enantiomers by NMR methods using chiral shift reagents.

It has been reported[49-51] that fluorinated lanthanide chelates

are superior to nonfluorinated shift reagents in producing larger differential shifts for given enantiomeric pairs. The chiral shift reagent employed in this work was tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium III (abbreviated as Facam; 135).



(135)

In ^{1}H NMR studies, this chiral shift reagent (135), when used in a 0.1 molar ratio (shift reagent/ligand) with (±)-6β-tropanol, produces a distinct lanthanide induced shift (Δδ) of the N-Me and the C6-H resonances (see Fig. 38a and Table 10). Lanthanide induced shift of other proton resonance is also observed. However, because of considerable overlapping and broadening of the signals, it is difficult to assign these shifted resonances. The only easily measured differential shift is from C6-H (ΔΔδ = 0.17), (see Fig. 38a). The differential shift of the N-Me group in the diastereomeric adduct at the 0.1 molar ratio (facam/(±)-6β-tropanol) is very small (ΔΔδ = 0.02), (Fig. 38a). Therefore, the C6-H resonance is crucial in the determination of optical purity of the enantiomers of 6β-tropanol when ^{1}H NMR is employed.

In the presence of facam (0.1 molar ratio), both ^{1}H NMR spectra of (+)-6β-tropanol and (-)-6β-tropanol show discrete C6-H resonance at δ4.65 and δ4.67 respectively (Fig. 37a and Fig. 37b). When equal

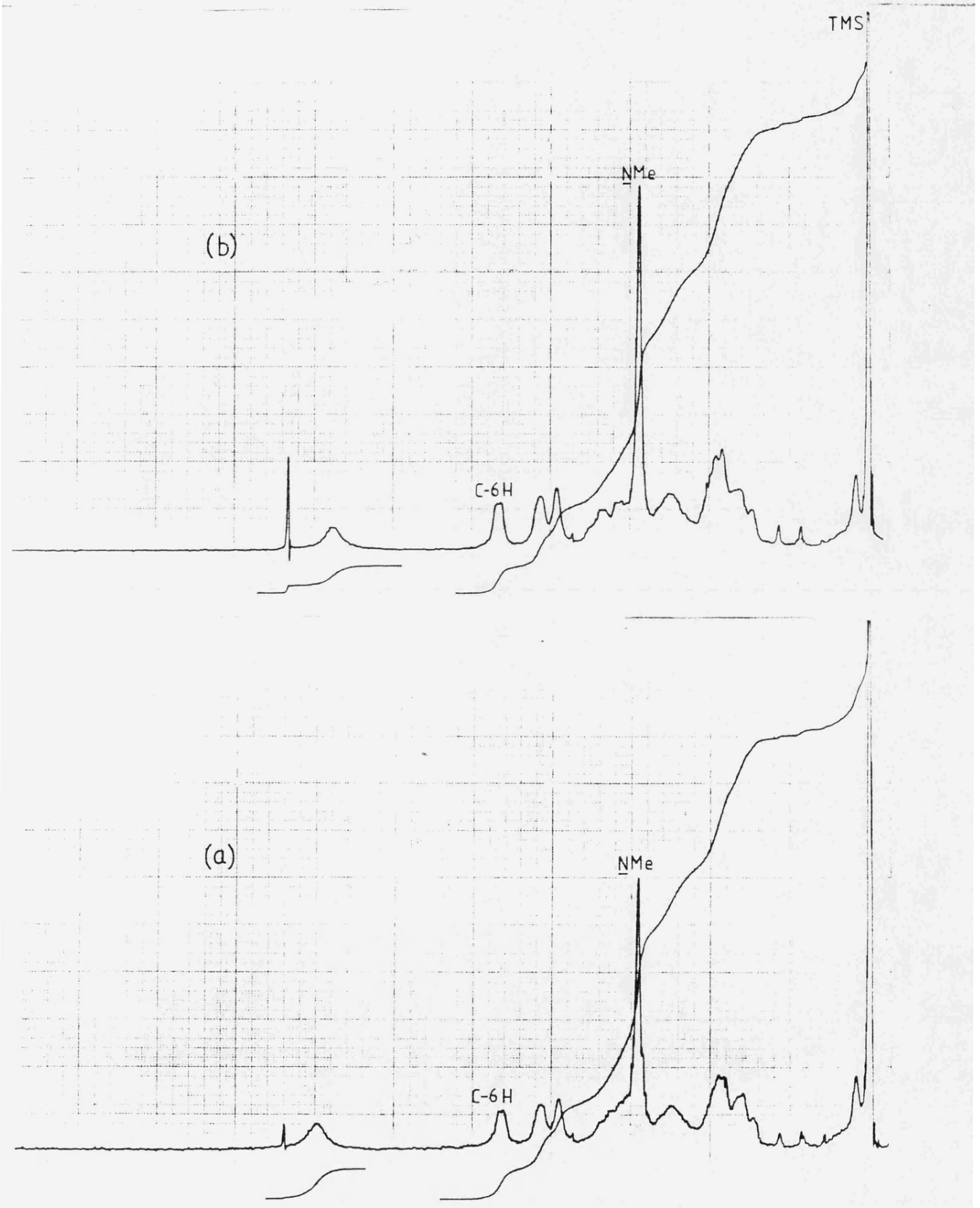


Fig. 37. ^{1}H NMR spectrum, (a) (+)-6β-tropanol and facam (135) in $CDCl_3$; (b) (-)-6β-tropanol and facam (135) in $CDCl_3$.

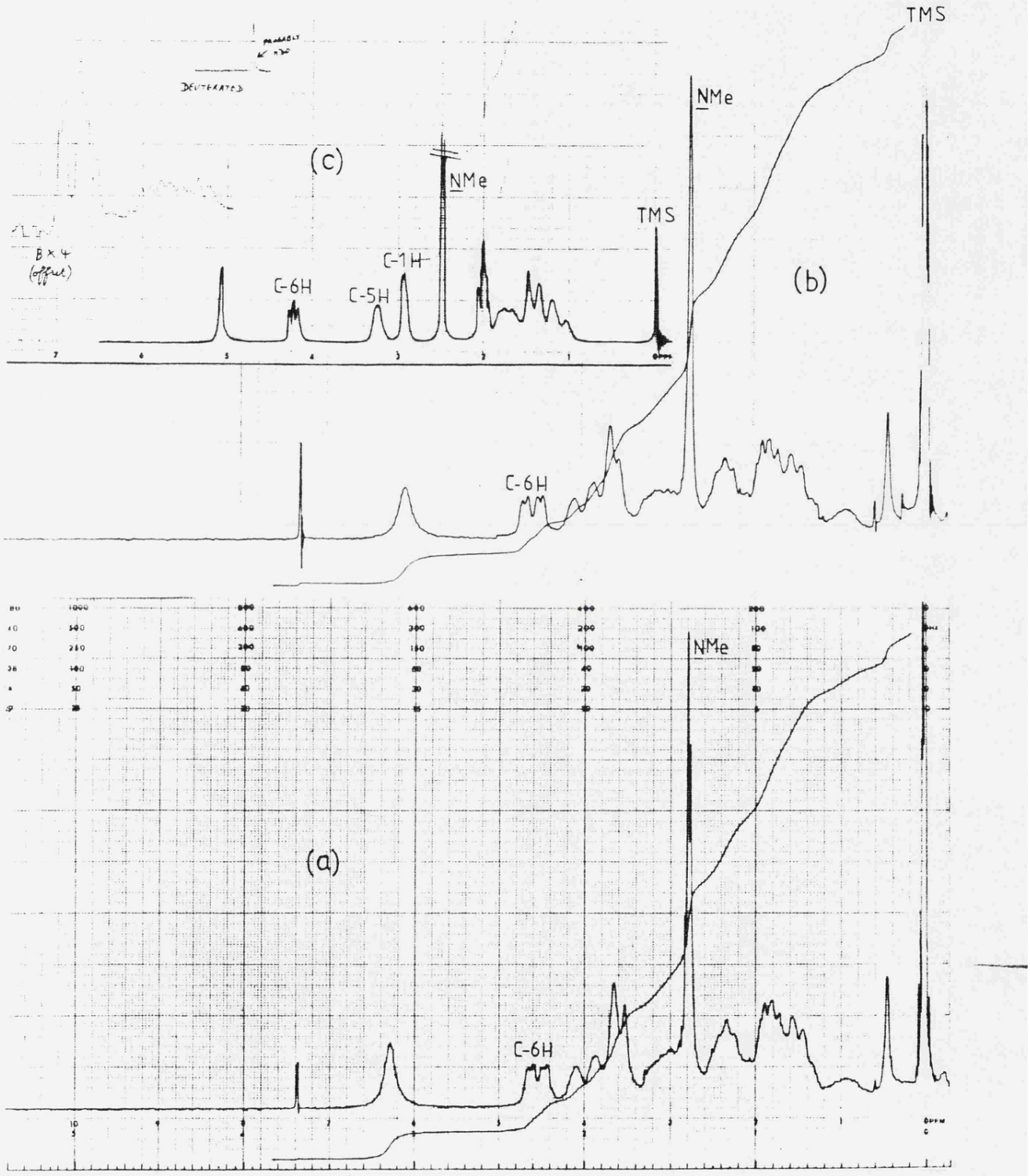


Fig. 38. ^{1}H NMR spectrum, (a) racemic (±)-6β-tropanol (51) and facam (135) in $CDCl_3$; (b) a 50/50% mixture of (+)- and (-)-6β-tropanol with facam (135) in $CDCl_3$; (c) (±)-6β-tropanol in $CDCl_3$ (without facam).

amounts of the (+)- and (-)-forms with facam (0.1 molar ratio) are mixed together and subjected to ^{1}H NMR analysis, the two C6-H resonances, corresponding to the two diastereomeric adducts, are observed ($\Delta\Delta\delta$ = 0.18), with equal integral ratio and same spectral characteristics as in the case when (±)-6β-tropanol is used (Fig. 38b).

Therefore, preliminary determination of the optical purity of (+)- and (-)-6β-tropanols using ^{1}H NMR indicated that the two isolated enantiomers were of reasonable purity.

The use of ^{13}C NMR in the determination of enantiomeric purity appears to be superior to the use of ^{1}H NMR. This is due to the fact that ^{13}C resonances enjoy much greater freedom from overlap than do proton resonances[52]. Additionally, the use of shift reagents in ^{13}C NMR does not cause serious line broadening which occurs with ^{1}H NMR. Nevertheless, one major disadvantage of FT ^{13}C NMR is that the intensities of particular resonances can vary enormously and thus has certain limitations in accurate quantitative measurements.

In the presence of facam (0.1 molar ratio), five double lines corresponding to the differential shift of five ^{13}C resonances are observed for (±)-6β-tropanol. Among these, the $\Delta\Delta\delta$ of C-6 is the largest (0.7 p.p.m.; see Fig. 40a and Table 11). When the (+)- and (-)-enantiomers are treated individually under the same conditions as the racemate, each enantiomer gives five singlets corresponding to the five double lines observed when racemic 6β-tropanol is used (Fig. 39a, Fig. 39b and Table 11).

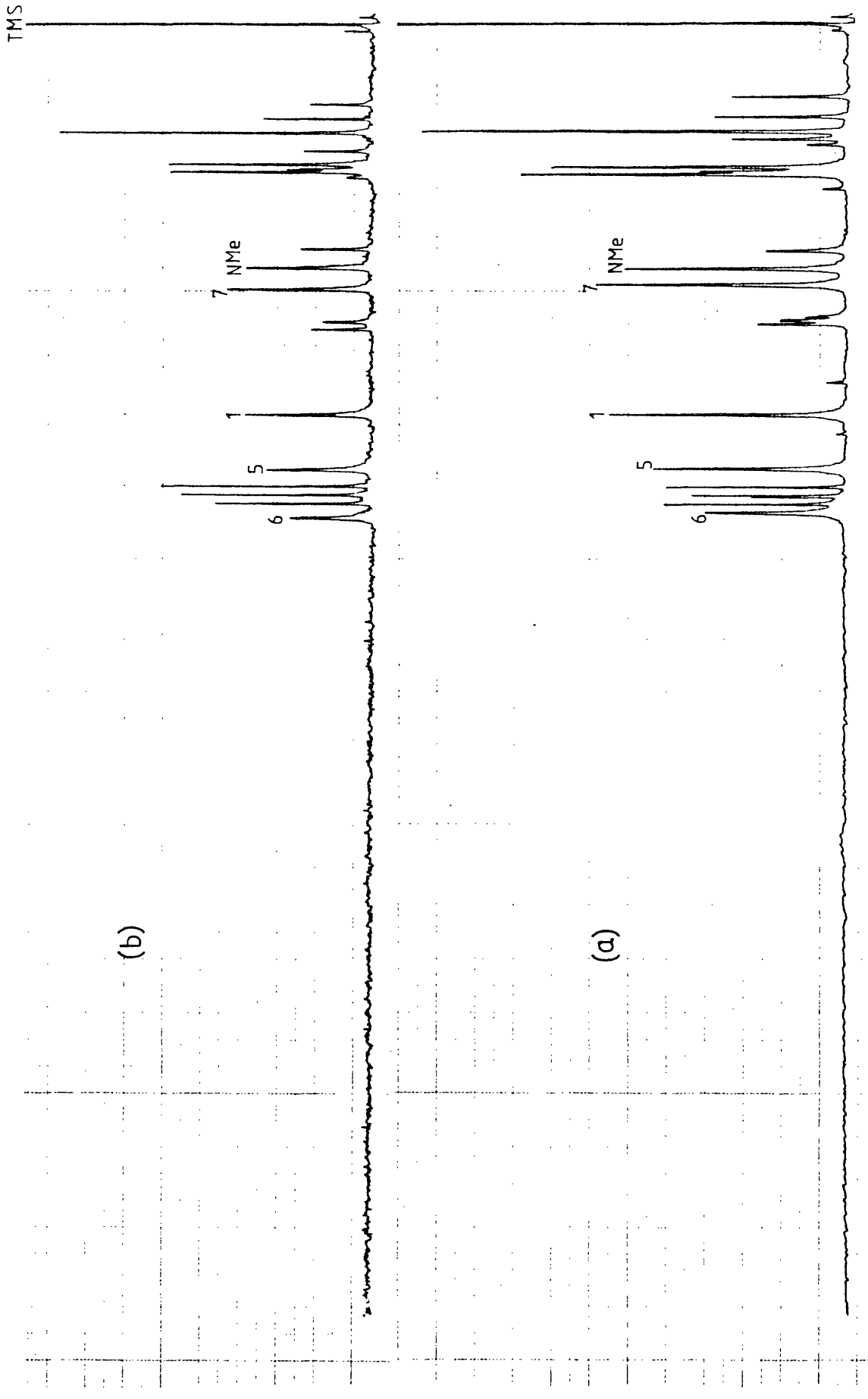


Fig. 39. ^{13}C NMR spectrum, (a) (+)-6β-tropanol and facam (135) in $CDCl_3$; (b) (-)-6β-tropanol and facam (135) in $CDCl_3$

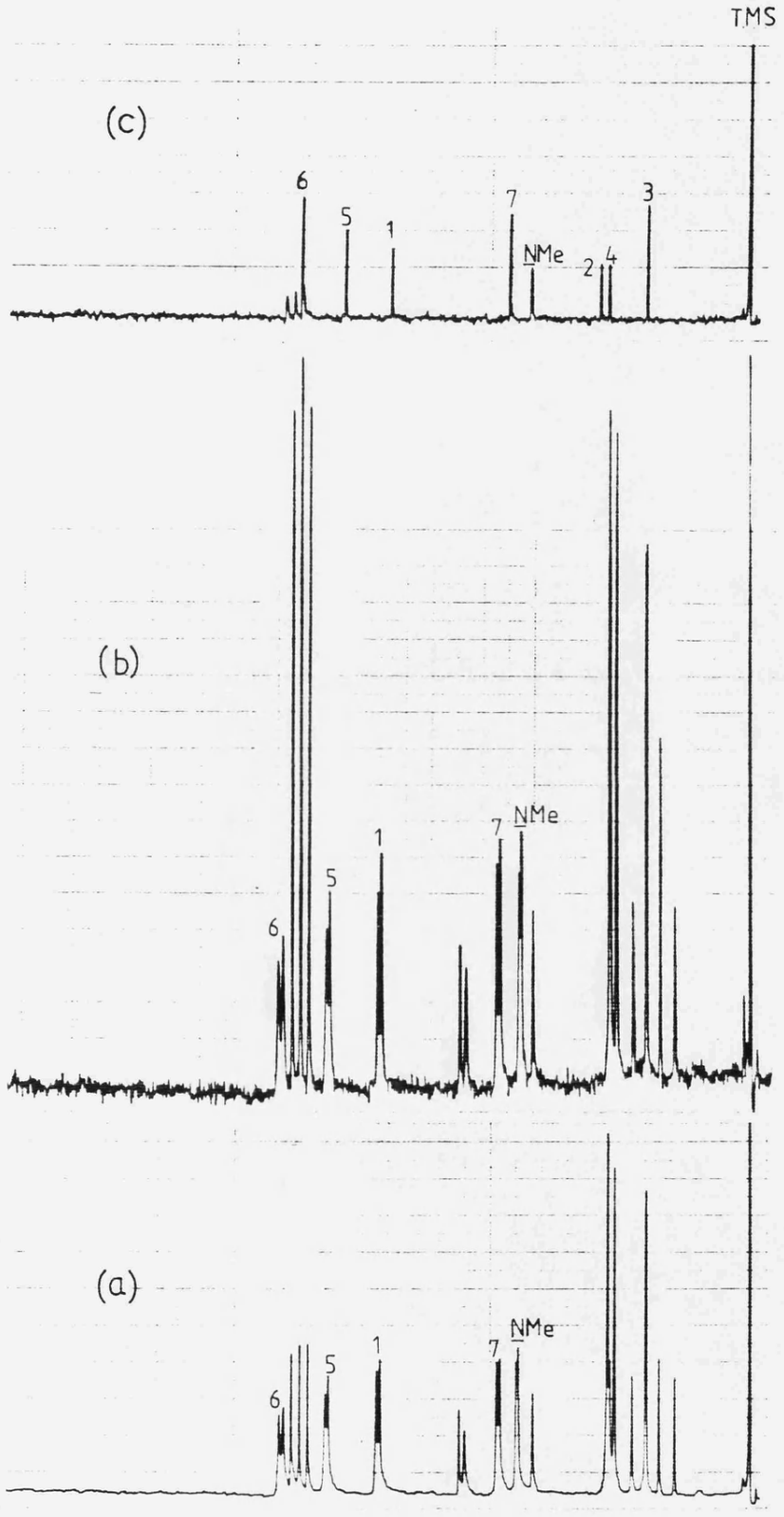


Fig. 40. ^{13}C NMR spectrum, (a) racemic (±)-6β-tropanol (51) and facam (135) in $CDCl_3$; (b) a 50/50% mixture of (+)- and (-)-6β-tropanol with facam (135) in $CDCl_3$; (c) (±)-6β-tropanol in $CDCl_3$ (without facam).

Table 10. ^{1}H NMR Shift Parameters (p.p.m.) induced by Facam (135) for 6β-Tropanols.

Compound	Solvent	Molar ratio (Facam/Ligand)	C6-H	N-Me	Shift Parameter
(±)-6β-Tropanol (51)	$CDCl_3$	0.0	4.26	2.49	δ
(±)-6β-Tropanol (51)	$CDCl_3$	0.1	0.17	0.02	ΔΔδ
(+)-6β-Tropanol (51a)	$CDCl_3$	0.1	4.65 0.39 -0.02	2.92 0.43 0.02	δ Δδ ΔΔδ
(-)-6β-Tropanol (51b)	$CDCl_3$	0.1	4.67 0.41 0.02	2.90 0.41 -0.02	δ Δδ ΔΔδ
50/50 % mixture of (51a) and (51b)	$CDCl_3$	0.1	0.18	-	ΔΔδ

Table 11 ^{13}C NMR Shift Parameters (p.p.m.) induced by Facam (135) for 6β-Tropanols

Compound	Solvent	Molar ratio (Facam/Ligand)	C-6	C-5	C-1	C-7	N-Me	Shift Parameter
(±)-6β-Tropanol (51)	$CDCl_3$	0.0	75.95	68.48	60.51	40.41	36.84	δ
(±)-6β-Tropanol (51)	$CDCl_3$	0.1	0.70	0.49	0.54	0.49	0.33	ΔΔδ
(+)-6β-Tropanol (51a)	$CDCl_3$	0.1	80.56 4.61 -0.38	72.65 4.17 -0.16	63.49 2.98 -0.33	43.18 2.77 -0.27	39.55 2.71 -0.11	δ Δδ ΔΔδ
(-)-6β-Tropanol (51b)	$CDCl_3$	0.1	80.94 4.99 0.38	72.81 4.33 0.16	63.82 3.31 0.33	43.45 3.04 0.27	39.66 2.82 0.11	δ Δδ ΔΔδ
50/50% mixture of (51a) and (51b)	$CDCl_3$	0.1	0.70	0.54	0.54	0.54	0.33	ΔΔδ

Further identification of the two enantiomeric 6β-tropanols is possible by mixing equal amounts of the (+)- and (-)-forms with facam (0.1 molar ratio) followed by ^{13}C NMR analysis. The resulting spectrum (Fig. 40b) shows the presence of the five double lines having the same resonance positions as those of the racemic 6β-tropanol (see Fig. 40a) under identical conditions (see Fig. 40a and Fig. 40b and Table 11 for shift parameters).

Thus, it is concluded that ^{13}C NMR studies further confirm the enantiomeric purity of the (+)- and (-)-6β-tropanols isolated in this work, as indicated by the absence of second lines for each of the five resonances studied.

Examination of the ^{13}C NMR lanthanide induced shift parameters (Table 11) suggests that the chiral chelate (facam) interacts with the 6β-tropanol molecule through an exosteric-pseudocontact mechanism[52-56]. All the carbon atoms in the exosteric side experience significant lanthanide induced shifts ($\Delta\delta$). The largest $\Delta\delta$ observed are for C-6 and C-5 of 6β-tropanol (see Table 11), indicating the proximity of the europium complex to these carbons. For molecules containing more than one heteroatom, intramolecular competition of the heteroatoms for lanthanide was envisaged[53]. It was suggested that secondary amino alcohols associate with europium *via* the nitrogen atom, whereas tertiary amino alcohols associated with europium through the hydroxy function.

However, the author suggests that for the secondary alcohol 6β-tropanol, there is a predominance of association of europium

with the hydroxy function(Fig. 41), whereas in the ester 6β-acetyloxytropane (136), the nitrogen atom is involved in the association (Fig. 42). This hypothesis is supported by the fact that for (±)-6β-acetyloxytropane, distinct differential shifts of the carbon resonances were not observed unless a molar ratio (Facam/substrate) greater than 0.2 was employed. The fact that no double lines were observed for C-6 and that the lanthanide induced shift (Δδ) of C-6 in (136) is only +0.1 p.p.m. indicates there is virtually no association of the acetyloxy function with europium. In addition, it was observed that the differential shifts of C-2, and C-4 (ΔΔδ = 0.60 and 0.54 p.p.m. respectively) were significantly greater than that of C-1 and C-5 (ΔΔδ = 0.22 and 0.33 p.p.m. respectively). This implies that the europium complex may associate with the amino function of (136) from the axial side, giving it close proximity to C-2 and C-4 and inducing significant differential shifts (see Fig. 42 and Fig. 43).

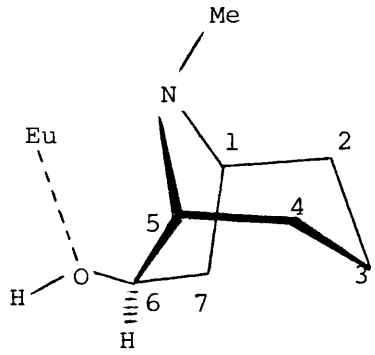


Fig. 41

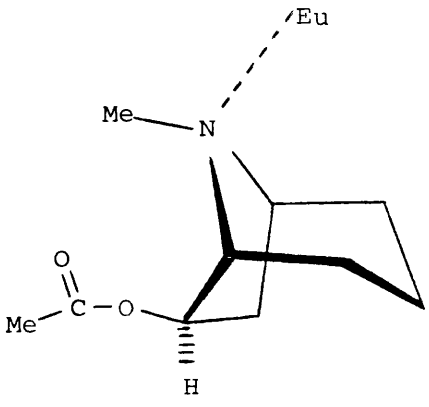


Fig. 42

In addition, the author observed that in both ^{1}H and ^{13}C NMR studies using the same molar ratio of chiral shift reagent, the apparent differential shifts* (ΔΔδ) of the enantiomers were much smaller than the virtual differential shifts of the equivalent

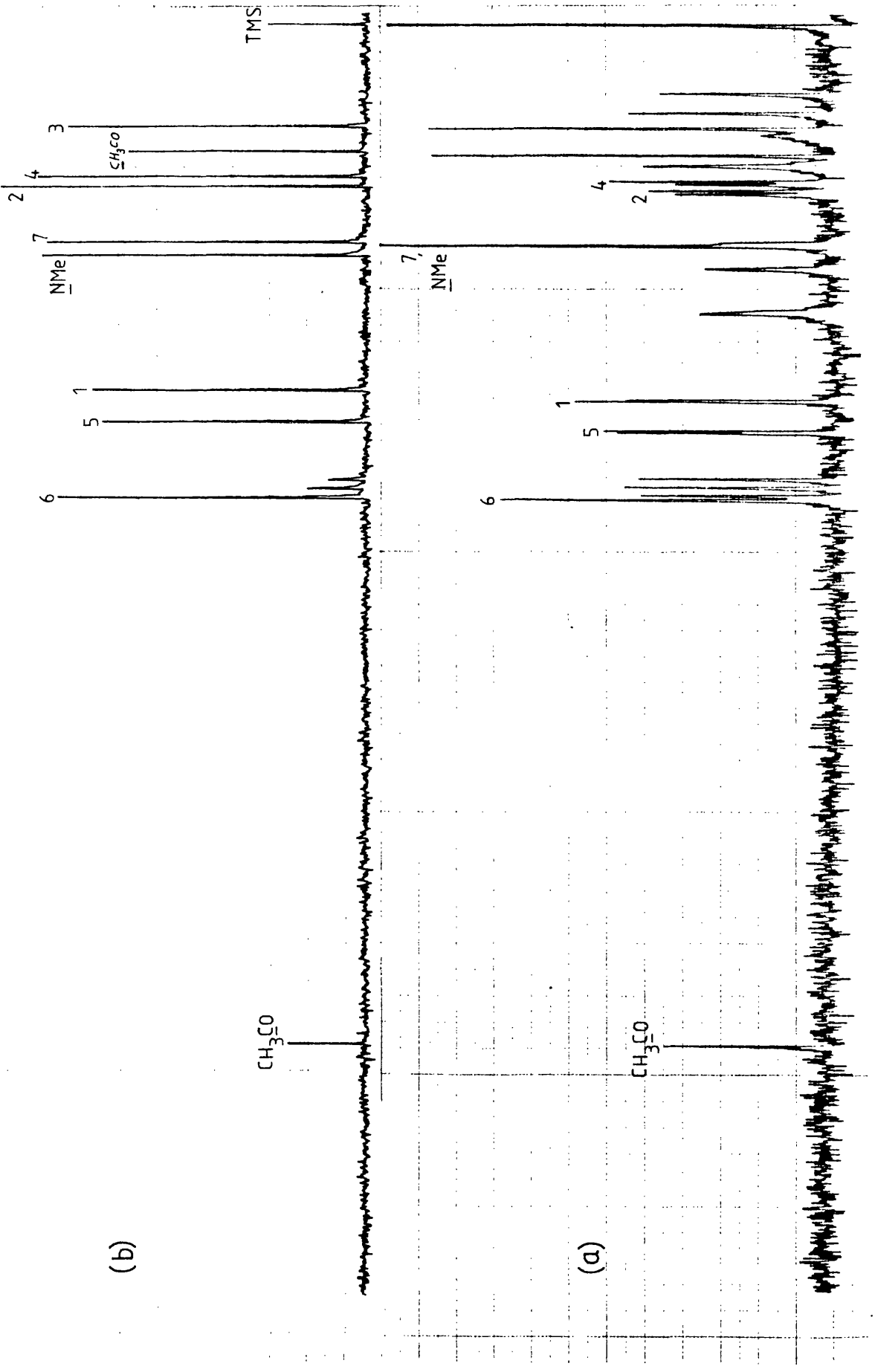


Fig. 43. ^{13}C NMR spectrum, (a) (±)-6β-acetyloxytropane (136) and facam (135) in $CDCl_3$; (b) (±)-6β-acetyloxytropane in $CDCl_3$ (without facam)

nuclei observed for the racemate (see Table 10 and Table 11). ^{1}H NMR shift parameter studies show that for C6-H, the ratio of the virtual differential shift of the racemate to the apparent differential shift* of the enantiomers is as great as 9:1 (see Table 10). On the other hand, from ^{13}C NMR shift parameter studies, this ratio of differential shifts between equivalent carbons ranges from about 1.6:1 to 3.1:1 (see Table 11). This significant difference between virtual differential shift and apparent differential shift is attributed to a further interaction between the two diastereomeric adducts in solution, such that the diastereotopic properties of each adduct are further augmented. The origin of this interaction is not clear, but it is hoped that this preliminary observation will prompt further investigation.

* Apparent differential shift: The difference of lanthanide induced shift ($\Delta\delta$) of equivalent nuclei of each enantiomer.

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5. Experimental

^{1}H NMR spectra were recorded on a J.E.O.L. P.S. 100 instrument operating at 100 MHz and 2.349 Tesla unless otherwise stated. ^{13}C NMR spectra were recorded on a J.E.O.L. FX 90X Fourier Transform NMR spectrometer operating at 22.9 MHz. TMS was used as internal standard unless otherwise stated.

Infrared spectra were obtained on a Pye Unicam S.P. 2000 instrument and, unless stated otherwise, were obtained on liquid films or KCl/KBr discs for solids.

Melting points were recorded on a Townson and Mercer apparatus unless otherwise stated. The apparatus was calibrated by standards.

5.1 Ketones

5.1.1 6β-Hydroxy-8-methyl-8-azabicyclo[3,2,1]octan -3-one (6β-Hydroxytropinone, 49; P.28)

2,5-Dimethoxy-2,5-dihydrofuran (53 gm) was dissolved in hydrochloric acid (2.9 N; 720 ml) and the mixture left standing for 18 hours at room temperature. The resulting light brown solution was neutralized with NaOH (6N; 360 ml) and then added to a solution of acetonedicarboxylic acid (120 gm), methylamine hydrochloride (55.8 gm) and anhydrous sodium acetate (280 gm) in water (2.8 litres). The solution was adjusted to pH 4.0 - 5.0 with hydrochloric acid (3N) and left standing at room temperature for 2 days. Potassium carbonate (950 gm) and sodium chloride (300 gm) were added to the dark brown mixture with stirring, and the solution was extracted continuously with ether (5 litres; flame-proof laboratory!) with exclusion of light. The ethereal extract was washed with water (120 ml), dried ($MgSO_4$) and evaporated to give light yellow crystals (22.0 gm; 35%) Recrystallization from isopropanol afforded 6β-Hydroxy-8-methyl-8-azabicyclo[3,2,1]octan -3-one, m.p. 121 - 122°C (Lit.[1,2] m.p. 121 - 122°C).

ν_{max} : 3200, 3000, 1700 cm^{-1}; $\delta_H(CDCl_3)$: 1.70 - 2.97 (6H, m, C2-H, C4-H, C7-H); 2.62 (3H, S, N-Me); 3.33 (1H, m, C1-H); 3.54 (1H, m, C5-H); 4.02 (2H, m, C6-H and O-H; reduces to 1 H on deuteration).

5.1.2 8-Methyl-8-azabicyclo[3,2,1]octan -6-one (Tropan-6-one, 52; P.33)

This was prepared by removal of the carbonyl function of 6β-hydroxytropinone (49) by Wolff-Kishner reduction, followed by oxidation with chromic acid, as previously described (Lit.[3]).

5.1.3 1-Benzoylethane (Phenyl vinyl ketone; 57; P.37)

Dimethylamine hydrochloride (15.0 gm), paraformaldehyde (7.0 g) and acetophenone (22.0 gm) were dissolved in ethanol (80 ml) and concentrated hydrochloric acid (0.4 ml) added. The resulting solution was refluxed for 3 hours and allowed to cool to room temperature to give N,N-dimethyl-2-benzoylethylamine hydrochloride as a white crystalline precipitate (27.0 gm; 70%), (Lit.[4,5] m.p. 156°C). A portion of this precipitate (2.2 gm) was dissolved in K_2CO_3 solution (40%, 15 ml), extracted with ether (2 x 100 ml), dried ($MgSO_4$) and evaporated to give N,N-dimethyl-2-benzoylethylamine, as a clear oil (1.8 gm).

δ_H ($CDCl_3$; 60 MHz): 2.24 (6H, S, N-Me); 2.53 - 3.49 (4H, m, $-CH_2CH_2-N$) 7.16 - 8.09 (5H, m, Ar-H)

N,N-dimethyl-2-benzoylethylamine (1.7 gm) was dissolved in acetone (20 ml) and methyl iodide (2 ml) added. The solution was left standing at room temperature for 3 hours. The precipitate which formed was filtered off and washed with acetone (2 x 10 ml), to give N,N-dimethyl-2-benzoylethylamine methiodide (2.51 gm), m.p. 199 - 200°C (decomp.). The methiodide (2.39 gm) was dissolved in 10% K_2CO_3 solution (20 ml), extracted with chloroform (3 x 100 ml), washed with water (2 x 50 ml), dried ($MgSO_4$) and evaporated to give 1-benzoylethene (0.9 gm; 91%) as a clear oil with a characteristic sweet odour.

δ_H ($CDCl_3$; 60MHz): 5.71-6.64 (2H, m, C2-H); 6.89-7.27 (1H, m, C1-H); 7.31-8.20 (5H, m, Ar-H).

5.2 Secondary alcohols.

5.2.1 (±)-6β-Hydroxy-8-methyl-8-azabicyclo[3,2,1]octane

(6β-Tropanol, 51; P.31)

This was prepared from 6β-hydroxytropinone (49) as previously described[3,6].

5.2.2 (+)- and (-)-6β-Hydroxy-8-methyl-8-azabicyclo[3,2,1]octane.

(P.87)

(±)-6β-Tropanol (51) was recrystallised 3 times from acetone. Pure 6β-tropanol (12.8 gm) and (+)-camphorsulphonic acid (21.5 gm) were dissolved in a mixture of acetone (160 ml) and isopropanol (70 ml), and the solution was left standing at room temperature for 4 days. The salt that crystallized (12.7 gm; 75%) was recrystallized from the same solvent mixture to give (+)-6β-Tropanol-(+)-camphorsulphonate (5.3 gm) as white rhomboidal plates, m.p. 241 - 243°C, $[\alpha]_D^{22}$ = + 26.4 (*c* 6.2, ethanol).

Found: C, 57.89; H, 8.35; N, 3.72%

$C_{18}H_{31}NO_5S$ requires: C, 57.86; H, 8.37, N, 3.75%.

A solution of the above camphorsulphonate salt (3.0 gm) was basified with NH_4OH (35%; 15 ml), extracted with ether (2 x 200ml) dried ($MgSO_4$) and the solvent evaporated to afford (+)-6β-tropanol (1.0 gm). Treatment of the free base with ethereal HCl afforded (+)-6β-Tropanol hydrochloride (1.0 gm), $[\alpha]_D^{22}$= + 2.4 (*c* 9.4, ethanol).

The mother liquor left after separation of the camphorsulphonate was concentrated *in vacuo*, treated with NH_4OH (35%; 90 ml), and the

liberated base extracted with ether (2 x 250 ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give colourless crystals (6.0 gm). A portion (5.8 gm) of this crystalline material and (+)-tartaric acid (6.9 gm) were dissolved in a mixture of methanol (67 ml) and absolute ethanol (27 ml) and the solution allowed to stand for 2 days. (-)-6β-Tropanol-(+)-tartrate separated as colourless rhomboidal crystals (8.31 gm), m.p. 174 - 175°C, $[\alpha]_D^{22}$ = +11.1 (*c* 7.6, ethanol).

Found: C, 49.42; H, 7.27; N, 4.95%

$C_{12}H_{21}NO_7$ requires: C, 49.46; H, 7.27; N, 4.81%.

The free base (-)-6β-Tropanol, obtained by basification of the tartrate salt followed by extraction in the usual way, was treated with etherealHCl to give (-)-6β-Tropanol hydrochloride, $[\alpha]_D^{22}$ = -2.3 (*c* 10.0, ethanol).

5.3 Tertiary alcohols

5.3.1 6β-Hydroxy-8-methyl-6β-phenyl-8-azabicyclo[3,2,1]octane

(6β-Phenyl-6α-tropanol, 53; R = H; P.33)

Bromobenzene (29.8 gm) in dry tetrahydrofuran (100 ml) was added dropwise to magnesium (5.2 gm) with stirring. The mixture was warmed until reaction commenced. Tropan-6-one (8.5 gm) in dry tetrahydrofuran (100 ml) was added dropwise to the Grignard mixture and the solution refluxed for 6 hours. After cooling, ether (300 ml) was added. 3N HCl (120 ml) was added dropwise to the mixture, with cooling and stirring, until complete solution. The organic layer was separated from the aqueous layer, and the former was washed with water (2 x 40 ml). The combined aqueous layers were washed with ether

(2 x 70 ml), basified with ammonia and extracted with ether (2 x 700 ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give light yellow plates (11.1 gm; 84%). Recrystallization from hexane afforded 6α-Hydroxy-8-methyl-6β-phenyl-8-azabicyclo[3,2,1]octane as needles, m.p. 97 - 98°C (Lit.[7]; hydrochloride, m.p. 235 - 236°C, C, H, N, analysed).

ν_{max} (free base): 3450, 3100, 1500, 760, 710 cm^{-1}

$\delta_H(CDCl_3)$: 0.84 - 2.80 (9H, m, C2-H, C3-H, C4-H, C7-H and O-H ; reduces to 8H on deuteration); 2.47 (3H, s, N-Me); 3.06 (1H, m, C5-H); 3.25 (1H, m, C1-H); 7.00 - 7.70 (5H, m, Ar-H).

The methiodide was prepared (Lit.[3], m.p. 280 - 282°C, C.H,N. analysed).

5.3.2 6α-Hydroxy-6β-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane (67; R = H; P.33)

m-Bromoanisole (7.5 gm) in dry tetrahydrofuran (25 ml) was added dropwise to magnesium (10 gm), with stirring. The mixture was warmed until reaction commenced. Tropan-6-one (1.3 gm) in dry tetrahydrofuran (25 ml) was added dropwise over 15 minutes and the mixture refluxed for 2 days. The Grignard complex was decomposed and the resulting solution treated as described above for the preparation of (53) to give 6α-Hydroxy-6β-(3-methoxyphenyl)-8-methyl-8-azabicyclo-[3,2,1]octane as an oil (1.78 gm; 77%).

ν_{max}: 3080, 2950, 1735, 1600, 1580, 1490, 810, 785, 770, 698 cm^{-1}

$\delta_H(CDCl_3$; 60 MHz): 0.70 - 2.60 (8H, m, C2-H, C3-H, C4-H, C7-H); 2.47 (3H, s, N-Me); 2.93 - 3.40 (2H, m, C1-H and C5-H); 3.78 (3H, s, ArO-Me); 6.55 - 7.43 (4H, m, Ar-H).

The hydrochloride crystallized from isopropanol, and had m.p. 210-212°C.

Found: C, 63.36; H, 7.96; N, 4.72%

$C_{15}H_{22}NO_2Cl$ requires:C,63.46;H, 7.82; N, 4.94%

5.3.3 6α-Hydroxy-6β-(4-methoxyphenyl)-8-methyl-8-azabicyclo-[3,2,1]octane (68; R = H; P.33)

The procedure described above for the synthesis of (67) was repeated using p-bromoanisole instead of m-bromoanisole. 6α-Hydroxy-6β-(4-methoxyphenyl)-8-methyl-8-azabicylo[3,2,1]-octane was obtained as an oil (79%).

ν_{max} 3460, 3100, 1605, 1580, 1510, 855, 835, 810 cm^{-1}.

δ_H($CDCl_3$; 60 MHz); 0.80 - 2.70 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.46 (3H, s, N-Me); 2.90 - 3.50 (2H, m, C1-H and C5-H) 3.75 (3H, s, ArO-Me); 6.60 - 7.74 (4H, m, Ar-H).

The hydrochloride crystallised from isopropanol, and had m.p. 198 - 200°C (Lit[7] m.p. 204 - 205°C).

Found: C, 63.20; H. 7.84; N. 4.96%

$C_{12}H_{22}NO_2Cl$ requires: C, 63.46; H, 7.82; N, 4.94%

5.3.4 6α-Hydroxy-6β-(3,4-dimethoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane (66; R = H; P.33)

The procedure described in Section 5.3.2 was repeated using 4-bromoveratrole instead of m-bromoanisole to give 6α-Hydroxy-6β-(3,4-dimethoxyphenyl)-8-methyl-8-azabicyclo-[3,2,1]octane (66) as an oil (54.%).

ν_{max}: 3550, 3100, 2980, 1605, 1590, 1515, 810, 790, 760 cm^{-1}.

δ_H ($CDCl_3$: 60 MHz): 0.90 - 2.80 (8H, m, C2-H, C3-H, C4-H, and C7-H); 2.48 (3H, s, N-Me); 2.95 - 3.50 (2H, m, C1-H and C5-H); 3.84 3.84 (3H, s, ArO-Me), 3.86 (3H, s, ArO-Me), 6.70 - 7.50 (3H, m, Ar-H).

The hydrochloride crystallized from isopropanol, and had m.p. 193 - 194°C.

Found: C, 60.85; H. 7.88; N. 4.34%

$C_{16}H_{24}NO_3Cl$ requires: C, 61.22; H, 7.71; N, 4.47%

5.3.5 6α-Hydroxy-6β-phenyl-8-azabicyclo[3,2,1]octane (54; 6β-phenyl-6α-nortropanol; P.35)

6β-Phenyl-6α-tropanol (53; R = H; 16.9 gm) trichloroethyl chloroformate (20.6 gm) and K_2CO_3 (6.0 gm) were dissolved in dry toluene (300 ml). The mixture was refluxed for 2 days, cooled and mixed with ether (1,000 ml). The solution was washed with sodium

hydroxide (5N, 2 x 200 ml) and then with water (3 x 150 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to give a gum. Acetic acid (90 %, 500 ml) and powdered zinc (34 gm) were added to the gum and the solution stirred at room temperature overnight. The mixture was basified with ammonia (ca 600 ml) and extracted with ether (3 x 700 ml). The combined ether extracts were washed with water (2 x 80 ml) dried ($MgSO_4$) and evaporated to afford 6α-Hydroxy-6β-phenyl-8-azabicyclo[3,2,1]octane as light yellow crystals (8.5 gm; 52%). Recrystallization from acetone gave the nortropanol (54) as colourless rhomboidal crystals, m.p. 145 - 146°C.

δ_H(DMSO-d_6): 1.00 - 2.50 (10H, m, C2-H, C3-H, C4-H, C7-H, O-H and N-H; reduces to 8 H on deuteration); 2.97 (1H, m, C1-H); 3.45 (1H, m, C5-H); 7.00 - 7.80 (5H, m, Ar-H).

Found: C, 76.79; H, 8.44; N, 6.90%

$C_{13}H_{17}NO$ requires: C, 77.15; H, 8.47; N, 6.89%.

5.3.6 8-(2-Benzoylethyl)-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]-octane (55; R = H; P.37)

6β-Phenyl-6α-nortropanol (54; 0.8 gm) was dissolved in dry toluene (6 ml) and phenyl vinyl ketone (57; 1 gm) added. The solution was refluxed overnight and evaporated. The oily residue was dissolved in ether (150 ml) and extracted with 0.2 N HCl (2 x 50 ml). The aqueous layer was washed with ether (3 x 60 ml), basified with K_2CO_3 (30%, 60 ml), and extracted with chloroform (3 x 100 ml). The chloroform layer was separated, dried ($MgSO_4$) and evaporated to afford 8-(2-Benzoylethyl)-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]-octane as an oil which crystallized slowly on standing.

ν_{max}: 3550, 3080, 2950, 1685, 1595, 1580, 1495, 755, 700 cm^{-1}

δ_H ($CDCl_3$; 60 MHz): 1.00 - 3.00 (10H, m, C2-H, C3-H, C4-H, C7-H and N-CH_2-); 3.00 - 3.20 (2H, t, -CH_2COPh); 3.00 - 3.53 (2H, m, C1-H and C5-H); 6.95 - 8.05 (10H, m, Ar-H).

5.3.7 8-(2-Cyanoethyl)-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]octane (56; R = H, P.37)

6β-Phenyl-6α-nortropanol (54; 0.75 gm) was dissolved in acrylonitrile (8.0 ml) and absolute ethanol (1.5 ml). The mixture was refluxed for 2 days, concentrated in vacuo, dissolved in ether (300 ml), and extracted with hydrochloric acid (1N; 25 ml). The aqueous layer was washed with ether (50 ml), basified with ammonia and extracted with ether (2 x 150 ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give 8-(2-Cyanoethyl)-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]octane as an oil (0.81 gm; 86%) which crystallized on standing.

ν_{max}: 3530, 3100, 2950, 2260, 1600, 1495, 755, 710 cm^{-1}.

δ_H($CDCl_3$; 60 MHz): 1.00 - 3.00 (8H, m, C2-H, C3-H, C4-H, C7-H, and -CH_2-CN); 3.04 (2H, t, N-CH_2), 2.87 - 3.63 (2H, m, C1-H and C5-H); 7.15 - 7.95 (5H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether and had m.p. 217 - 219°C.

Found: C, 65.83; H, 7.29; N, 9.78%

$C_{16}H_{21}N_2OCl$ requires: C, 65.61; H, 7.23; N, 9.57%.

5.3.8 6α-Hydroxy-6βphenyl-8-(2-phenylethyl)-8-azabicyclo[3,2,1]octane (60; R = H; P.41)

Phenylacetyl chloride (1.3 gm) was added dropwise to a solution of 6β-phenyl-6α-nortropanol (54; 0.8 gm) and triethylamine (4.8 gm), in ether (100 ml) and tetrahydrofuran (23 ml). The solution was refluxed for 6 hours, cooled and ether (400 ml) added. The solution was filtered, and the filtrate was washed with water (3 x 50 ml) dried ($MgSO_4$) and evaporated to give an oil (1.27 gm).

ν_{max}: 3495, 3050, 1630, 1500, 740, 680 cm^{-1}

A solution of the oil (1.27 gm) in dry ether (200 ml) was added over 15 minutes, with stirring, to a mixture of lithium aluminium hydride (3.0 gm) in dry ether (100 ml). The resulting mixture was refluxed for 5 hours, cooled, and water (10.5ml) NaOH (4N ; 2.25 ml) added dropwise with cooling and stirring. The mixture was filtered, and the filtrate washed with water (2 x 25 ml), dried ($MgSO_4$) and evaporated to give 6α-Hydroxy-6β-phenyl-8-(2-phenylethyl)-8-aza-bicyclo[3,2,1]octane as an oil (0.48 gm; 40%)

ν_{max}: 3500, 3100, 3000, 1600, 1495, 730, 680 cm^{-1}.

δ_H($CDCl_3$, 60 MHz): 0.90 - 3.60 (14H, m, C1-H, C2-H, C3-H, C4-H, C5-H, C7-H and N-(CH_2)$_2$-); 7.05 - 7.75 (10 H, m, Ar-H).

The hydrochloride crystallised from acetone and had m.p. 227 - 228°C.

5.3.9 8-Allyl-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]octane

(62; R = H; P.41)

Allyl bromide (0.95 gm) was added dropwise to a mixture of 6β-phenyl-6α-nortropanol (54: 1.2 gm) and K_2CO_3 (2.0 gm) in absolute ethanol (90 ml), with stirring. The resulting mixture was refluxed for 2 days, cooled and ether (200 ml) added. The mixture was filtered

and the filtrate washed with water (2 x 20 ml), dried ($MgSO_4$) and evaporated to give 8-Allyl-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]-octane as an oil (1.28 gm; 89%) which crystallized slowly on standing.

ν_{max}: 3500, 3120, 2950, 1635, 1595, 1490, 745, 690 cm^{-1}.

δ_H ($CDCl_3$; 60 MHz): 1.00 - 2.85 (8H, m, C2-H, C3-H, C4-H, and C7-H); 3.00 - 3.60 (4H, m, C1-H, C5-H, and N-CH_2-); 4.85 - 5.40 (2H, m, -C=CH_2); 5.50 - 6.20 (1H, m, -CH=C-); 7.00 - 7.90 (5H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether and had m.p. 217 - 219°C.

Found: C, 68.41; H, 7.91; N, 4.94%

$C_{16}H_{22}NOCl$ requires: C, 68.66; H, 7.93; N, 5.01%

5.3.10 8-Cyclopropylmethyl-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]-octane (61; R = H; P.41)

Cyclopropanecarboxylic acid chloride (0.86 gm) in dry ether (15 ml) was added dropwise, with stirring, to a solution of 6β-phenyl 6α-nortropanol (0.8 gm) and triethylamine (4.0 gm) in dry ether (70 ml). The solution was refluxed for 24 hours, cooled, filtered and evaporated. The oily residue was dissolved in ether (400 ml), washed with water (2 x 40 ml), dried ($MgSO_4$) and evaporated to give an oil (1.32 gm).

ν_{max}: 3440, 3100, 3000, 1720, 1620, 1480, 755, 695 cm^{-1}. The oil (1.32 gm) was treated with lithium aluminium hydride (3.7 gm) by the same procedure described in section 5.3.8. 8-Cyclopropylmethyl-6α-hydroxy-6β-phenyl-8-azabicyclo[3,2,1]octane was obtained as an oil (0.92 gm; 78%).

ν_{max} : 3470, 3100, 2950, 1595, 1490, 770, 695 cm^{-1}.

δ_H ($CDCl_3$): 0.00 - 1.27 (5H, m, cyclopropyl protons); 1.20 - 2.45 (8H, m, C2-H, C3-H, C4-H, and C7-H); 2.66 (2H, m, -N-CH_2-); 3.29 (1H, m, C1-H); 3.47 (1H, m, C5-H); 7.00 - 8.10 (5H, m, Ar-H).

5.4 Esters

5.4.1 (+)- and (-)-6β-Acetyloxy-8-methyl-8-azabicyclo[3,2,1]octane P.89)

(+)-6β-Tropanol (0.4 gm) was dissolved in a mixture of acetic anhydride (0.6 gm) and triethylamine (0.4 gm) and left standing at room temperature overnight. The reaction mixture was treated with K_2CO_3 solution (10%; ca 10 ml) followed by ethereal extraction (5 x 100 ml). The ethereal extracts were washed with water (2 x 20 ml), dried ($MgSO_4$) and evaporated to give (+)-6β-Acetyloxy-8-methyl-8-azabicyclo[3,2,1]octane as an oil (0.41 gm; 79%).

δ_H($CDCl_3$; 60 MHz); 1.00 - 2.30 (8H, m, C2-H, C3-H, C4-H, C7-H); 2.02 (3H, s, CH_3-CO); 2.47 (3H, s, N-Me); 5.11 (1H, m, C6-H).

This oil (0.41 gm) was dissolved in acetone (30 ml) and iodomethane (2 ml) added. The solution was left standing for 3 hours and (+)-6β-Acetyloxy-8-methyl-8-azabicyclo[3,2,1]octane methiode separated as white crystals (0.5 1 gm; 74%), m.p. 255 - 256°C.

Found: C, 40.56; H, 6.25: N, 4.30%

$C_{11}H_{20}NO_2I$ requires: C, 40.61; H, 6.20; N, 4.31%

The same esterification procedure described above was repeated using (-)-6β-tropanol (0.38 gm) to afford (-)-6β-Acetyloxy-8-methyl 8-azabicyclo[3,2,1]octane as an oil (0.39 gm; 79%).

δ_H ($CDCl_3$; 60 MHz): 1.00 - 2.30 (8H, m, C2-H, C3-H, C4-H, C7-H);

2.02 (3H, s, CH_3-CO); 2.47 (3H, s, N-Me); 5.11 (1H, m, C6-H).

This oil (0.39 gm) was dissolved in acetone (25 ml) and iodomethane (2 ml) added. The solution was left standing for 3 hours and (-)-6β-Acetyloxy-8-methyl-8-azabicyclo[3,2,1]octane methiodide separated as white crystals (0.49 gm; 74%), m.p. 253 - 254°C.

Found: C, 40.37; H, 6.27; N, 4.27%

$C_{11}H_{20}NO_2I$ requires: C, 40.61; H, 6.20; N, 4.31%

5.4.2 6α-Acetyloxy-8-methyl-6β-phenyl-8-azabicyclo[3,2,1]octane (53; R = acetyl; P.47) and 8-methyl-6β-phenyl-6α-propionyloxy-azabicyclo 3,2,1 octane (53; R = propionyl; P.47)

The tertiary alchol (53; R = H; 1.0 gm) and p-toluenesulphonic acid (0.2 gm) were dissolved in acetic anhydride (15 ml) and heated at 110° for 4 days. The solution was concentrated in vacuo, cooled and basified with saturated $KHCO_3$ solution (20 ml).The resulting solution was extracted with ether (3 x 70 ml), washed with water (2 x 10 ml), dried ($MgSO_4$) and evaporated to give 6α-Acetyloxy-8-methyl-6β-phenyl-8-azabicyclo[3,2,1]octane as an oil (1.1 gm; 92%).

ν_{max}: 3100, 2920, 1740, 1600, 1495, 755, 695 cm^{-1}.

$\delta_H(CDCl_3)$; 0.84 - 2.92 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.05 (3H, s, CH_3CO); 2.50 (3H, s, N-Me); 3.27 (1H, m, C1-H); 3.64 (1H, m, C5-H); 7.00 - 7.60 (5H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether as white crystals, m.p. 204 - 206°C.

Found: C, 64.71; H, 7.61; N, 4.69%

$C_{16}H_{22}NO_2Cl$ requires: C, 64.95; H, 7.50; N, 4.74%

Reaction of the tertiary alcohol (53; R = H) with propionic anhydride using the same procedure as described above, afforded 8-Methyl-6β-phenyl-6α-propionyloxy -8-azabicyclo[3,2,1]octane as an oil (88%).

ν_{max}: 3130, 2990, 1740, 1600, 1495, 795, 680 cm^{-1}.

$\delta_H(CDCl_3$; 60 MHz): 0.90 - 1.35 (3H, t, $C\underline{H}_3-CH_2-CO$); 1.00 - 2.90 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.25 - 2.50 (2H, q, $-C\underline{H}_2-CO$); 2.48 (3H, s, N-Me); 3.22 (1H, m, C1-H); 3.62 (1H, m, C5-H); 7.05 - 7.63 (5H, m, Ar-H)

The hydrochloride crystallized from ethanol-ether, and had m.p. 188 - 189°C (Lit.[7] m.p. 186 - 187°C, C, H, N analysed). The material is hygroscopic.

The 6α-acetate (53; R = acetyl), 6α-propionate (53; R = propionyl) were also prepared by the in situ esterification method described in the following section.

5.4.3 6α-Acetyloxy-6β-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]-octane (67; R 2 acetyl; P.48)

Tropan-6-one (52; 1.2 gm) was refluxed for 2 days with the Grignard reagent prepared from m-bromoanisole (5.2 gm) and magnesium (0.7 gm) in tetrahydrofuran (60 ml). The solution was cooled in ice-bath and a solution of acetic anhydride (5.5 ml) in ether (15 ml) added. The mixture was stirred for 1 hour, poured into crushed ice and acetic acid (5.5 ml) was added. The resulting mixture was stirred at 10°C for 2 days. The aqueous layer was washed with ether (3 x 60 ml), basified with K_2CO_3 solution (30%) and extracted with ether (2 x 150 ml)

The combined ether layer was washed with water (2 x 25 ml), dried ($MgSO_4$) and evaporated to give 6α-Acetyloxy-6β-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane as an oil (1.14 gm; 43%).

ν_{max}: 3080, 2950, 1735, 1600, 1580, 1490, 810, 785, 770, 698 cm^{-1}

$\delta_H(CDCl_3)$: 0.75 - 2.85 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.03 (3H, s, CH_3-CO); 2.49 (3H, s, N-Me); 3.37 (1H, m, C1-H); 3.59 (1H, m, C5-H); 3.73 (3H, s, ArO-Me); 6.60 - 7.30 (4H, m, Ar-H).

The hydrochloride crystallized from isopropanol and had m.p. 196 - 198°C.

Found: C, 62.67; H, 7.43; N, 4.13%

$C_{17}H_{24}NO_3Cl$ requires: C, 62.64; H, 7.43; N, 4.30%

5.4.4 6α-Acetyloxy-6β-(4-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]-octane (68; R = acetyl; P.48)

The tertiary alcohol (68; R = H) was acetylated by the in situ esterification method (section 5.3.2) to afford 6α-Acetyloxy-6β-(4-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane as an oil (61 %).

ν_{max}: 3080, 2950, 1730, 1610, 1580, 855, 835, 810 cm^{-1}.

$\delta_H(CDCl_3)$: 0.79 - 2.90 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.03 (3H, s, CH_3-CO); 2.47 (3H, s, N-Me); 3.23 (1H, m, C1-H); 3.58 (1H, m, C5-H); 3.74 (3H, s, ArO-Me); 6.60 - 7.40 (4H, m, Ar-H).

The hydrochloride crystallized from isopropanol, had m.p. 184 - 186°C.

Found: C, 62.50; H, 7.50; N, 4.14%

$C_{17}H_{24}NO_3Cl$ requires: C, 62.64; H, 7.43; N, 4.30 %

5.4.5 6α-Acetyloxy-6β-(3,4-dimethoxyphenyl)-8-methyl-8-azabicyclo-[3,2,1]octane (66; R = acetyl; P.47)

The tertiary alcohol (66; R = H; 0.7 gm), triethylamine (0.7 gm), 4-dimethylaminopyridine (0.015 gm) and acetic anhydride (1.1 gm) were mixed and stirred at room temperature for 12 hours. The reaction mixture was basified with K_2CO_3 solution (10%; 15 ml), extracted with ether (3 x 100 ml), washed with water (2 x 20 ml), dried ($MgSO_4$) and evaporated to give 6α-Acetyloxy-6β-(3,4-dimethoxyphenyl)-8-methyl-8-azabicylo[3,2,1]octane as an oil (0.7 gm; 87%). The tertiary alcohol (66; R = H) could also be satisfactorily esterified by the in situ esterification method (Section 5.3.2)

ν_{max}: 3100, 2970, 1735, 1610, 1590, 1510, 810, 795, 765 cm^{-1}.

δ_H ($CDCl_3$): 0.90 - 2.93 (8H, m, C2-H, C3-H, C4-H, and C7-H); 2.06 (3H, s, CH_3-CO); 2.52 (3H, s, N-Me); 3.28 (1H, m, C1-H); 3.65 (1H, m, C5-H); 3.85 (6H, 2 x s, ArO-Me); 6.70 - 7.20 (3H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether and had m.p. 175 - 176°C.

Found : C, 60.51; H, 7.49; N, 3.90%

$C_{18}H_{26}NO_4Cl$ requires: C, 60.73; H, 7.37; N, 3.94%

5.4.6 6α-Acetyloxy-8-(2-benzoylethyl)-6β-phenyl-8-azabicyclo[3,2,1]-octane (55; R = acetyl; P.47)

The tertiary alcohol (55; R = H; 0.34 gm) was acetylated by the procedure described in section 5.4.5 to afford 6α-Acetyloxy-8-(2-bezoylethyl)-6β-phenyl-8-azabicylo[3,2,1]octane as an oil (0.3 gm; 78%)

ν_{max}: 3080, 2940, 1740, 1690, 1595, 1580, 1495, 760, 690 cm^{-1}.

δ_H ($CDCl_3$): 1.00 - 3.00 (10H, m, C2-H, C3-H, C4-H, C7-H, and N-CH_2-); 2.08 (3H, s, CH_3-CO); 3.00 - 3.54 (3H, m, -CH_2-COPh, C1-H); 3.58 (1H, m, C5-H); 6.95 - 7.70 (10H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether, and had m.p. 168 - 170°C.

Found: C, 68.96; H. 6.87; N, 3.25%

$C_{24}H_{28}NO_3Cl$ requires: C, 69.62; H, 6.82, N, 3.36%

5.4.7 6α-Acetyloxy-8-(2-cyanoethyl)-6β-phenyl-8-azabicyclo[3,2,1]-octane (56; R = acetyl; P.48)

The tertiary alcohol (56; R = H ; 0.81 gm) was acetylated by the same procedure described in section 5.4.5. to afford 6α-Acetyloxy-8-(2-cyanoethyl .)-6β-phenyl-8-azabicyclo[3,2,1]octane as an oil (0.88 gm; 93%)

ν_{max}: 3100, 2960, 2260, 1730, 1600, 1500, 760, 700 cm^{-1}.

δ_H ($CDCl_3$; 60 MHz): 0.90 - 2.90 (10H, m, C2-H, C3-H, C4-H, C7-H, and CH_2-CN); 2.08 (3H, s, CH_3-CO); 2.90 - 3.25 (2H, m, N-CH_2-); 3.30 - 3.80 (2H, m, C1-H and C5-H); 7.10 - 7.70 (5H, m, Ar-H).

The hydrochloride crystallized from isopropanol, and had m.p. 178 - 180°C.

Found: C, 64.84; H, 7.01; N, 8.13%

$C_{18}H_{23}N_2O_2Cl$ requires: C, 64.57; H, 6.92; N, 8.37%

5.4.8 6α-Acetyloxy-6β-phenyl-8-(2-phenylethyl)-8-azabicyclo[3,2,1]-octane (60; R = acetyl; P.48)

The tertiary alcohol (60; R = H; 1.16 gm) was acetylated by the same procedure described in section 5.4.5 to afford 6α-Acetyloxy-

6β-phenyl-8-(2-phenylethyl)-8-azabicyclo[3,2,1]octane as an oil (1.0 gm; 76%).

ν_{max}: 3050, 2950, 1730, 1600, 1495, 760, 700 cm^{-1}.

δ_H($CDCl_3$; 60 MHz); 0.90 - 3.20 (12H, m, C2-H, C3-H, C4-H, C7-H, N-CH_2- and -CH_2-Ph); 2.04 (3H, s, CH_3-CO); 3.37 (1H, m, C1-H); 3.64 (1H, m, C5-H); 7.00 - 7.60 (10H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether, and had m.p. 194-196°C.

Found: C, 71.30; H, 7.41; N, 3.82%

$C_{23}H_{28}NO_2Cl$ requires: C, 71.56; H, 7.32; N, 3.63%

5.4.9 6α-Acetyloxy-8-allyl-6β-phenyl-8-azabicylo[3,2,1]octane (62; R = acetyl; P.48)

The tertiary alcohol (62; R = H; 1.69 gm) was acetylated by the procedure described in section 5.4.5 to afford 6α-Acetyloxy-8-allyl-6β-phenyl-8-azabicylo[3,2,1]octane as an oil (1.72 gm; 87%).

ν_{max}: 3100, 2950, 1735, 1640, 1600, 1500, 760, 700 cm^{-1}.

δ_H($CDCl_3$): 0.90 - 2.95 (8H, m, C2-H, C3-H, C4-H, and C7-H); 2.07 (3H, s, CH_3-CO); 3.35 (1H, m, C1-H); 3.42 (2H, m, N-CH_2-); 3.68 (1H, m, C5-H); 4.94 - 5.80 (2H, m, -C=CH_2); 5.60 - 6.04 (1H, m, -CH=C-); 7.00 - 7.50 (5H, m, Ar-H).

The hydrochloride crystallized from acetone and had m.p. 177 - 179°C.

Found: C, 66.91; H, 7.56; N, 4.27%

$C_{18}H_{24}NO_2Cl$ requires: C, 67.15; H, 7.52; N, 4.36 %

5.4.10 6α-Acetyloxy-8-cyclopropylmethyl-6β-phenyl-8-azabicyclo[3,2,1]-octane (61; R = acetyl; P.48)

The tertiary alcohol (61; R = H; 0.79 gm) was acetylated by the procedure described in section 5.4.5 to afford 6α-Acetyloxy-8-cyclopropylmethyl-6β-phenyl-8-azabicyclo[3,2,1]octane as an oil (0.8 gm; 87%).

ν_{max}: 3100, 2960, 1735, 1600, 1500, 760, 700 cm^{-1}.

δ_H($CDCl_3$; 60 MHz): 0.00 - 0.65 (5H, m, cyclopropyl protons); 1.00 - 2.60 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.05 (3H, s, CH_3-CO); 2.64 (2H, m, N-CH_2-); 3.43 (1H, m, C1-H); 3.86 (1H, m, C5-H); 7.00 - 7.70 (5H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether, and had m.p. 192 - 194°C.

Found: C, 67.93; H, 7.88; N, 4.19%

$C_{19}H_{25}NO_2Cl$ requires: C, 67.93; H, 7.81; N, 4.17%

5.5 6-Phenyl-6-tropene (107) and its reduction products.

5.5.1 6-Phenyl-8-methyl-8-azabicyclo[3,2,1]oct-6-ene (107; 6-Phenyl-6-tropene; P.104)

6β-Phenyl-6α-tropanol (53; R = H; 4.0 gm) was dissolved in ethanolic HCl and evaporated. The oily residue was refluxed with thionyl chloride (6.6 gm) in chloroform (60 ml) for 2 hours, during which vigorous evolution of SO_2 was observed. The solvent and excess thionyl chloride were evaporated and alcoholic KOH (100 ml) added. The mixture was refluxed overnight. The resulting brown solution was filtered and the filtrate concentrated in vacuo. Water (50 ml) was added and the emulsion extracted with ether (3 x 200 ml). The

ethereal extracts were washed with water (3 x 30 ml), dried ($MgSO_4$) and evaporated to give 6-Phenyl-8-methyl-8-azabicyclo[3,2,1]oct-6-ene as a light brown oil (2.74 gm; 75%) b.p. 120°C / 0.5 mm Hg. (Lit.[7] hydrochloride, m.p. 195 - 196°C).

ν_{max} (free base): 3120, 2950, 1590, 1495, 750, 735, 680 cm^{-1}.

$\delta_H(CDCl_3)$; 1.00 - 2.10 (6H, m, C2-H, C3-H, C4-H); 2.30 (3H, s, N-Me); 3.52 (1H, m, C1-H); 3.76 (1H, m, C5-H); 6.20 (1H, d, C7-H); 7.00 - 7.60 (5H, m, Ar-H).

5.5.2 6α-Phenyl-8-methyl-8-azabicyclo[3,2,1]octane (120; 6α-Phenyl-tropane; P.109)

6-Phenyl-6-tropene (107; 0.5 gm) in absolute ethanol (25 ml) was hydrogenated over palladium charcoal (0.27 gm) at 50 p.s.i. in a rocking Parr apparatus at room temperature for 16 hours. The mixture was filtered and the filtrate evaporated to give 6α-Phenyl-8-methyl-8-azabicyclo[3,2,1]octane as an oil (0.5 gm; 99%).

ν_{max}: 3060, 2950, 1600, 1500, 775, 760, 700, 680 cm^{-1}.

$\delta_H(CDCl_3)$: 0.87 - 2.68 (8H, m, C2-H, C3-H, C4-H and C7-H); 2.64 (3H, s, N-Me); 3.34 (2H, m, C1-H and C5-H); 3.86 (1H, m, C6-H); 7.00 - 7.60 (5H, m, Ar-H).

The hydrochloride crystallized from ethanol-ether, and had m.p. 216 - 218°C.

Found: C, 66.05; H, 8.64; N, 5.47%

$C_{14}H_{20}NCl.H_2O$ requires: C, 65.72 ; H, 8.67; N, 5.48%

The methiodide (126) crystallized from acetone, and had m.p. 302 - 304°C.

$\delta_H(DMSO\text{-}d_6)$: 1.00 - 3.00 (8H, m, C2-H, C3-H, C4-H and C7-H); 3.28 (6H, s, $\overset{+}{N}$-Me); 3.89 - 4.37 (3H, m, C1-H, C5-H, C6-H); 7.10 - 7.60

(5H, m, Ar-H).

Found: C, 52.55; H, 6.25; N, 4.16%

$C_{15}H_{22}NI$ requires: C, 52.47; H, 6.46; N, 4.08%

5.5.3 4-Methylamino-2-phenylcycloheptene (123; P.117)

6-Phenyl-6-tropene (107; 5.6 gm) in dry tetrahydrofuran (100 ml) was added dropwise with stirring, to lithium aluminium hydride (4.2 gm) in dry tetrahydrofuran (200 ml). The reaction mixture was refluxed for 12 hours, cooled, and water (15 ml) and NaOH (5N, 3.3 ml) added successively, with cooling and stirring. The mixture was filtered and the filtrate dried ($MgSO_4$) and evaporated to afford an oil (4.95 gm; 88%). Treatment of the resulting oil with ethereal HCl and crystallization from isopropanol afforded 4-Methylamino-2-phenylcycloheptene hydrochloride as white rhomboidal crystals, m.p. 171 - 173°C.

ν_{max} (free base): 3080, 2950, 1600, 1500, 760,700cm^{-1}.

δ_H($CDCl_3$; free base): 1.00 - 2.40 (5H,m, C5-H, C6-H and N-H; reduces to 4H on deuteration); 1.96 (2H, m, C7-H); 2.42 (3H, s, N-Me); 2.54 (1H, m, C4-H); 2.69 (2H, m, C3-H); 6.13 (1H, t, C1-H); 6.90 - 7.60 (5H, m, Ar-H).

δ_C ($CDCl_3$; free base):

Aliphatic ^{13}C: 24.3 (OFR, t; C-6), 28.4 (OFR, t, C-5); 34.1 (OFR, q; N-Me); 38.3 (OFR, t; C-3); 38.8 (OFR, t; C-7); 57.5 (OFR, d; C-4); 131.1 (OFR, d; C-1); 140.6 (OFR, s; C-2).

Aromatic ^{13}C: 125.7 (OFR, d; C-2' and C-6'); 126.4 (OFR, d; C-4'); 128.2 (OFR, d; C-3' and C-5'); 144.8 (OFR, s; C-1').

ms m/e: 201 (23); 186 (3); 170 (11); 158 (20); 142 (6); 128 (10); 115 (9); 96 (3); 91 (8). 83 (20); 70 (100); 57 (22).

Accurate mass on molecular ion,

Found: 201.1503

$C_{14}H_{19}N$ requires: 201.1513

Found: C, 70.69; H, 8.53; N, 5.71%

$C_{14}H_{20}NCl$ requires: C, 70.70; H, 8.48; N, 5.90%

5.5.4 3-Deutero-4-methylamino-2-phenylcycloheptene (125; P.118)

The procedure described in section 5.5.3 was repeated using lithium aluminium deuteride. 3-Deutero-4-methylamino-2-phenylcycloheptene was obtained as an oil (83%).

The hydrochloride crystallized from isopropanol as white rhomboidal crystals, and had m.p. 168 - 170°C.

δ_H($CDCl_3$; free base): 1.00 - 2.40 (5H, m, C6-H, C5-H and N-H; reduces to 4H on deuteration); 2.20 (2H, m, C7-H); 2.42 (3H, s, N-Me); 2.57 (1H, m, C4-H); 2.72 (1H, m, C3-H); 6.13 (1H, t, C1-H); 6.90 - 7.60 (5H, m, Ar-H)

δ_C ($CDCl_3$; free base):

Aliphatic ^{13}C: 24.3 (OFR, t; C-6); 28.5 (OFR, t; C-5); 34.1 (OFR, q; N-Me); [38.2 (t); OFR, m; C-3] ; 38.7 (OFR, t; C-7); 57.4 (OFR, d; C-4); 131.2 (OFR, d; C-1); 140.6 (OFR, s; C-2).

Aromatic ^{13}C: 125.8 (OFR, d; C-2 and C-6'); 126.4 (OFR, d; C-4'); 128.2 (OFR, d; C-3' and C-5'); 144.9 (OFR, s; C-1).

ms m/e: 202 (17); 171 (9); 159 (15); 143 (5); 129 (12); 115 (6); 91 (4); 83 (26); 70 (100); 57 (18).

Accurate mass on molecular ion.

Found: 202.1571

$C_{14}H_{18}DN$ requires: 202.1576.

5.5.5 4-Dimethylamino-2-phenylcycloheptene (127; P.119,128)

A. 6α-Phenyltropane methiodide (126; 1.6 gm) and potassium -t-butoxide (33 gm) were dissolved in absolute ethanol (150 ml) with stirring and cooling. The reaction mixture was refluxed for 48 hours, cooled and evaporated in vacuo. The syrup obtained was dissolved in the minimum volume of water and extracted with ether (3 x 120 ml). The ethereal extracts were washed with water (3 x 60 ml) dried ($MgSO_4$) and evaporated to give 4-Dimethylamino-2-phenylcyclo - heptene as a colourless oil. (0.92 gm; 91%).

ν_{max}: 3050, 2940, 1595, 1495, 755, 695 cm^{-1}.

δ_H ($CDCl_3$): 1.14 - 2.20 (4H, m, C6-H, C5-H); 2.10 (2H, m, C7-H); 2.31 (6H, s, N-Me); 2.52 (1H, m, C4-H); 2.65 (2H, m, C3-H); 6.12 (1H, t, C1-H); 7.00 - 7.60 (5H, m, Ar-H).

δ_C ($CDCl_3$):

Aliphatic ^{13}C: 26.0 (OFR, t; C-6); 28.4 (OFR, t; C-5); 34.0 (OFR, t; C-3); 34.9 (OFR, t; C-7); 40.7 (OFR, q; N-Me); 62.2 (OFR, d; C-4); 130.6 (OFR, d; C-1); 141.7 (OFR, s; C-2).

Aromatic ^{13}C: 125.7 (OFR, d; C-2' and C-6'); 126.4 (OFR, d; C-4'); 128.2 (OFR, d; C-3' and C-5'); 144.7 (OFR, s; C-1).

The hydrochloride crystallized from ethanol-ether and had m.p. 140 - 141°C.

Found: C, 69.19; H, 9.11; N, 5.50%

$C_{15}H_{22}NCl.\ \frac{1}{2}H_2O$ requires: C, 69.06; H, 8.89; N, 5.37%

B. 4-Methylamino-2-phenylcycloheptene (123; 0.29 gm) was mixed with aqueous formaldehyde (37 - 41%; 0.58 gm) and formic acid[8] (0.42 gm). The reaction mixture was refluxed for 5 hours, cooled basified with NaOH (2N) and extracted with ether (3 x 100 ml).

The ethereal extracts were washed with water (3 x 20 ml), dried ($MgSO_4$) and evaporated to give 4-Dimethylamino-2-phenylcycloheptene as a colourless oil (0.24 gm; 77%).

ν_{max}: 3050, 2940, 1595, 1495, 755, 695 cm^{-1}.

δ_H ($CDCl_3$): 1.10 - 2.20 (4H, m, C6-H, C5-H); 2.10 (2H, m, C7-H); 2.32 (6H, s, N-Me); 2.50 (1H, m, C4-H); 2.64 (2H, m, C3-H); 6.12 (1H, t, C1-H); 7.00 - 7.60 (5H, m, Ar-H).

δ_C ($CDCl_3$):

Aliphatic ^{13}C: 26.0 (OFR, t; C-6); 2.84 (OFR, t; C-5); 33.9 (OFR, t; C-3); 34.9 (OFR, t; C-7); 40.7 (OFR, q; N-Me); 62.2 (OFR, d; C-4); 130.6 (OFR, d; C-1); 141.7 (OFR, s; C-2).

Aromatic ^{13}C: 125.7 (OFR, d; C-2' and C-6'); 126.4 (OFR, d; C-4'); 128.2 (OFR, d; C-3' and C-5'); 144.7 (OFR, s; C-1').

The hydrochloride crystallized from ethanol-ether and had m.p. 138 - 140°C.

Found: C, 69.10; H, 9.03; N, 5.41%

$C_{15}H_{22}NCl.\frac{1}{2}H_2O$ requires: C, 69.06; H, 8.89; N, 5.37%.

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